The New England
Journal of Medicine

VOLUME 215 JULY 9, 1936 NUMBER 2

FLUID THERAPY IN SURGERY: A CRITICAL REVIEW*

BY JOHN D. STEWART, M.D.†

THE subject of water balance is appearing with increasing frequency in present medical literature, and interest in studying this widely important subject is now very properly being shown by the clinician as well as the physiologist and biochemist. All patients who are very sick are actual or potential problems in disturbed water and salt metabolism. The following discussion is presented in the hope that it will be useful to the clinician in dealing with the problem in fluid therapy, for there is still much variable and uncritical practice in treating such patients. This paper embodies principles and practices in active acceptance on the Surgical Services of the Massachusetts General Hospital and makes no pretense of being final or exhaustive. Inasmuch as general principles are being discussed, rather than specific contributions, no bibliography is appended. Those interested may find an excellent list of references to pertinent work on water metabolism in the book, "Body Water", by J. P. Peters (Charles C Thomas, 1935).

The fluids of the human body, which comprise roughly 70 per cent of its weight, may be considered as occupying three reservoirs; namely, the blood vessels, the interstitial areas and the cells. The blood vessels contain fluid amounting to about 9 per cent of the body weight, the interstitial areas (not including the blood) hold fluid approximating 16 per cent of the body weight, while the fluid within the cells throughout the body comprises 45 per cent of the body weight. The fluid of the body, whether in the blood stream, the interstitial reservoir or the cells, contains a constant proportion of salts, and this content of salt must be kept invariable within narrow limits or serious symptoms and death result. This proportion of salts is equivalent to 0.9 per cent sodium chloride solution, the so-called "physiological salt solution". The chief salts making up the salt content of the blood plasma and interstitial fluid are sodium chloride and sodium bicarbonate, while the chief ions within the cells are potassium and phosphate.

Not only must the total concentration of the salts in the body fluids be kept constant, but their normal relative quantities must be maintained. An abnormal increase or decrease in the alkaline salt sodium bicarbonate, for instance, at the expense of the neutral salt sodium chloride, will cause a change in body fluid reaction, i.e., alkalosis or acidosis. Therefore, in viewing derangement of body fluids there are three important considerations; namely, the total amount of fluid, secondly, the proper concentration of salts, and thirdly, the proper balance between acid and base. It is important to remember that the measurement of the concentration of an ion, such as sodium, chloride or bicarbonate, in the blood is an expression only of the proportion of the substance in relation to water, and gives no clue as to whether its total amount in the body is increased or decreased.

It is the function of the kidney to stand guard over the body fluids and effect the proper regulation of these factors. If too much salt is ingested, the excess is promptly excreted in the urine, and if either acid or base tends to predominate in the body fluids, the kidney helps to restore the balance by forming an acid or alkaline urine, depending on the need. This regulation of the amount and electrolyte pattern of the body fluids is perhaps the most pressing office of the kidney, and in fluid therapy a normal kidney may be relied upon to retain what the body needs and excrete the excess.

The proteins of the plasma constitute another factor to be considered in fluid metabolism. It is due to the osmotic pressure of these colloid substances that fluid is kept within the capillaries in balance against the force of the blood pressure. The normal level of plasma proteins is 6.5 to 7.5 per cent. If the proteins become lowered below approximately 5 per cent, as from chronic malnutrition, or from loss in large draining wounds or through the excretion of protein by the kidneys in nephrosis, generalized edema may result. Other factors of importance in the regulation of body fluid are blood pressure and capillary and cell wall permeability. In a general way one might say that the circulation of the blood, the plasma proteins and the condition of semipermeability of capillary and cell wall have to do with the distribution and proper partition of fluid within the organism, while the kidney, through the medium of

*From the Surgical Services of the Massachusetts General Hospital.

†Stewart, John D.—Assistant in Surgery, and Dalton Scholar, Massachusetts General Hospital. For record and address of author see "This Week's Issue," page 97.

the circulation, is concerned with maintaining the constancy of its composition and volume.

Routes Available in Fluid Therapy

1. By mouth: This route is adequate in healthy people and in most of the sick. There are certain circumstances, however, which make it necessary to resort to other channels. Some of these conditions are the following: (a) Organic disease of the gastrointestinal tract or peritoneum, in association perhaps with nausea, vomiting or diarrhea. (b) Functional derangement of the gastrointestinal tract, as in pernicious vomiting of pregnancy and many conditions in children, who may develop diarrhea and vomiting during the course of remote infections, such as otitis media. (c) Inability of the patient to co-operate, as in conditions of delirium or coma, and in infants. (d) Urgent conditions, wherein fluids are needed immediately and it is inadvisable to wait for possibly uncertain absorption from the intestinal canal, as in severe diabetic acidosis. (e) Conditions such as hemorrhage, shock, sepsis and chronic malnutrition in which blood is needed and must be given by vein. Also, if sodium chloride or sodium bicarbonate is needed, these are unpalatable to the sick. A procedure which is useful at times, as in partially occlusive lesions of the esophagus, is the administration of fluids through a rubber tube of calibre 12 or 14 French, introduced through the nose into the stomach. Such an inlying tube may be left in place for days and large quantities of water and nutrient materials may be introduced directly into the stomach or duodenum, using, if need be, a constant drip flow. Such a tube is likely to become irritating to the nasopharynx, however, and an unco-operative patient may refuse to leave it in place.

2. By rectum: Large quantities of water and physiological salt solution may be absorbed from the colon when introduced through the rectum. Experimental evidence tends to show that glucose is not absorbed from the colon, although variable quantities may be absorbed from the terminal ileum after regurgitation through the ileocecal valve. Glucose has the disadvantage that it may undergo fermentation in the colon and produce irritation leading to expulsion of fluid given subsequently. There seems to be no conclusive evidence that nutrient substances are ever absorbed from the colon itself. At any rate no hypertonic fluids should be administered by proctoclysis in dehydration, and if glucose is given it should be in 5 per cent solution. Fluids introduced into the colon through proctoclysis may be given in eight or ten ounce quantities in the adult every four hours, or the constant drip method, as originally popularized by Murphy, may be used. The disadvantages of this means of giving fluid to a patient are the rather slow and uncertain absorption, and the limitation of the type of fluid which may be given. However, in case of limited facilities and help, proctoclysis may be an invaluable method of supplying water, salt and heat to a sick patient.

3. Hypodermoclysis: This is one of the most useful methods in fluid therapy. Absorption is fairly rapid and is certain. Sterilized fluid must be given, of course, with aseptic technique. The bilateral subpectoral injection, using gravity force and allowing the fluid to run into the tissues slowly, may be used. An alternative site, indicated especially in conditions involving embarrassment of respiration, is the subcutaneous tissues of the inner or outer aspect of the thighs. Only fluids isotonic with the blood, or slightly hypertonic, should be given by hypodermoclysis, i.e., 0.9 per cent sodium chloride, 5 per cent glucose solution, 2½ per cent glucose in 0.9 per cent sodium chloride solution, or Ringer's solution. The skin at the point of insertion of the needle may be novocainized, and if desirable in further preventing discomfort, novocain may be added to the fluid being given in proportion of 300 milligrams per liter of fluid. In an adult patient a daily hypodermoclysis of up to two liters, may be given for several days. In a patient whose circulation, renal function and serum proteins are not deranged, sluggish absorption of fluid given by hypodermoclysis is evidence that an excess is being given.

The limiting factors in this mode of supplying fluid to the body are the discomforts produced by distention of tissues, even though slowly done, and the limitation of the kind of fluid which may be given. Sodium bicarbonate solution, the more concentrated glucose solutions, and, of course, blood cannot be given in this way.

4. Intraperitoneal injection: Physiological salt solution, 5 per cent glucose solution, Ringer's solution, and even whole blood, may be introduced into the peritoneal cavity, from which absorption may be rapid. This technique has been used particularly in infants whose veins are small and whose tissue areas may not be large enough to make hypodermoclysis practicable. Although the availability of this method is to be borne in mind, the procedure should rarely be resorted to, for it carries with it the danger of infection and traumatization of viscera and peritoneum. Absorption may be uncertain, particularly in the case of glucose solution or blood, and intractable distention of the abdomen has been observed as a sequel. Even the injection of physiological salt solution has been shown to evoke a richly cellular peritoneal exudate, the importance of which in the production of adhesions may be considerable.

5. Intravenous infusion: This therapeutic procedure is one of the most valuable in med-

icine and ranks with anesthesia and asepsis as a life-saving measure. The variety of fluids which may be given by vein is great, for dilution of the injected fluid is instantaneous. Hypertonic fluids such as 5 per cent sodium bicarbonate solution, 50 per cent glucose solution and 50 per cent sucrose solution and hypotonic fluids, even distilled water, may be given by vein, although the last is, of course, never to be used in fluid therapy. In addition, alkaline and acid fluids may be infused directly into the blood stream when needed. Sterile technique is necessary, of course, and the speed of the injection must be controlled. At least thirty minutes should be taken in giving a liter of fluid, and ordinarily the slow, gravity-drip technique is to be preferred. By splinting the extremity to avoid having the needle dislodged, fluid may be allowed to flow into a vein without stopping for as long as four or five days, the rate of flow being kept constant. When veins are small and obscured by fat, it is at times necessary to expose them under local anesthesia and tie a cannula in place.

Types of Fluid Used in Fluid Therapy

Concerning water itself as given by mouth or by rectal injection, nothing need be said except that water alone, without salt, will not repair dehydration.

1. Physiological salt solution: This solution, consisting of 0.9 per cent sodium chloride, is perhaps the most generally useful. It is isotonic with the blood and neutral in reaction, and may be given by any of the methods discussed. Sodium chloride is absolutely indispensable in the repair of dehydration, owing to the need for maintenance of the proper salt concentration in the body fluids. In fact, one may see the paradoxical spectacle of dehydration with diuresis where water without sodium chloride is taken in quantity by a dehydrated animal, for the kidney promptly excretes the excess water in order to avoid having the salts of the body diluted to a dangerous degree. In giving physiological salt solution we must keep in mind the fact that this fluid is readily retained to the point of producing edema, and the amount given should not be greatly in excess of the body need.

2. Glucose solutions: Isotonic (5 per cent) glucose solution may be given by vein or by hypodermoclysis, while hypertonic glucose solutions, such as the 10 per cent, 20 per cent, or 50 per cent solutions, must be given only by vein, for they are highly irritating to the tissues. Hypertonic glucose solutions are prone to evoke thrombosis of a vein at the point of injection unless mechanical trauma of the vein is avoided and the venous flow is rapid. Glucose is rapidly taken up by the liver and muscles after injection into the blood stream and is converted into glycogen or oxidized within a few hours. This leaves its water of solution free for elimination by the kidneys, and hence isotonic glucose solution has a diuretic effect. This diuretic effect is much to be desired at times in the oliguria of dehydration, for effective renal function is thus promoted. Hypertonic glucose solutions have an even greater diuretic effect, but are undesirable in treating dehydration since their first effect is to abstract water from cells already dehydrated.

A question of some interest is whether to give insulin in the nondiabetic when glucose solutions are being given intravenously. The weight of evidence seems to indicate that if 5 or 10 per cent glucose solution is given at a properly slow rate the nondiabetic needs no supplement of insulin in utilizing the glucose.

3. Glucose in physiological salt solution: A 2½ per cent, 5 per cent, or 10 per cent solution of glucose made up with 0.9 per cent sodium chloride may be useful for intravenous injection, since water, glucose and sodium chloride are all supplied. Such solutions are hypertonic, and thus are best given intravenously, rather than interstitially. Their hypertonicity also renders such solutions less desirable in severe dehydration, since their immediate effect would be to abstract water from cells.

4. Sucrose solution, 50 per cent: This strongly hypertonic, nontoxic solution may be given intravenously for the purpose of lowering intracranial pressure. Sucrose given by vein is quantitatively excreted through the kidneys, and thus has a strong diuretic effect. It possesses a great advantage over 50 per cent glucose solutions in lowering intracranial pressure in view of the fact that sucrose does not diffuse into the cerebrospinal fluid as does glucose with the production of a secondary rise in cerebrospinal fluid pressure.

5. Sodium bicarbonate solution, 5 per cent: Occasionally in treating severe acidosis with dehydration, as in diarrheal disease in infants and in diabetic acidosis, it is advisable to give sodium bicarbonate solution intravenously, as well as physiological salt solution. A solution of 5 per cent sodium bicarbonate in water is hypertonic and alkaline and must be given by vein rather than into the tissues. The great disadvantage that this solution has is the difficulty in sterilization. When heated, such a solution loses CO_2 and becomes changed into the very alkaline, toxic sodium carbonate. Therefore, unless special technique for sterilizing sodium bicarbonate solutions is available, these solutions can be given only without formal sterilization. Sodium bicarbonate may be taken from a fresh bottle of the chemically pure reagent with a sterile teaspoon and added directly to

a flask of glucose solution or physiological salt solution, which is to be given intravenously, in the proportion of one or two teaspoonfuls per 500 cc. of fluid. Although this practice has the sanction of extensive use, it cannot be wholly commended.

6. Sodium lactate solution 1.8 per cent (1/6 molar): The use of this fluid as a substitute for sodium bicarbonate solution, has been extensively advocated by A. F. Hartmann. It has the advantages of being isotonic and neutral, permitting interstitial as well as intravenous administration. In addition, its alkalinity results from the gradual conversion of lactate to glucose in the body, the glucose being available to meet the body's need. As one of the fluids used in the treatment of dehydration with acidosis, supplementary to physiological salt solution, this fluid has real merit, particularly in children, in whom interstitial injection may be desirable. Sodium lactate solution is contraindicated in dehydration with alkalosis.

7. Acacia solution: This solution, consisting, as usually given of 6 per cent gum arabic (U.S.P.) made up in 0.9 per cent sodium chloride solution, has a limited usefulness in the treatment of conditions of acutely reduced blood volume, such as shock and hemorrhage, when blood transfusion cannot immediately be done. Acacia forms a colloidal solution which leaves the blood stream very slowly and therefore tends to hold fluid in circulation. It should be run into a vein slowly, not exceeding 20 cc. per minute. Dangers are, injury to the hepatic parenchyma with enlargement of the liver and diminished excretion of bile salts and pigment and diminution in urine volume. Repeated injections are much more apt to cause harm, particularly from depression of serum proteins and damage to the polygonal cells of the liver. In an emergency, however, when it is not possible to give a blood transfusion immediately, the intravenous injection of acacia solution may be regarded as a temporary substitute. Its use is more justifiable in shock than in severe hemorrhage.

8. Blood: Blood as given in transfusion is obtained from a compatible donor and is injected in quantities varying from 400 to 1200 cc. in the adult. Whole, unmodified blood may be given from a paraffinized container in a technique rapid enough to avoid clotting; or, blood may be citrated and injected more slowly. Citrated blood is somewhat more likely to produce untoward reactions, but possesses the advantage of being much simpler to give. Indeed, such blood may be infused into a vein using the ordinary intravenous infusion technique and may be allowed to run in quite slowly. Blood which has been defibrinated, as by stirring or shaking with glass beads in order to remove the elements of the clot, should never be used for transfusion, since toxic substances are formed in such traumatization. This is one of the reasons why autotransfusion of blood which has collected in the peritoneal cavity is undesirable.

In general, the conditions in which fluid therapy is necessary are as follows:

I. Dehydration.
   (a) Without acidosis or alkalosis.
   (b) With acidosis.
   (c) With alkalosis.

II. Conditions requiring blood transfusion.
   (a) Acutely reduced blood volume.
   (b) Chronic anemia.
   (c) Lowered serum proteins.
   (d) Severe infections, acute or chronic.
   (e) Disease in which there is abnormal tendency to bleed.

III. Conditions to be treated with hypertonic fluid therapy.

Dehydration. Dehydration occurs when the intake of water and salts is insufficient, or when there is abnormal loss of body fluid, whether from vomiting or diarrhea or through the skin and lungs. Dehydration may be unaccompanied by acidosis or alkalosis, as exemplified by the dehydration of excessive sweating and some cases of severe diarrhea. Usually, however, in severe dehydration there is concurrent disturbance of the acid-base equilibrium in the body. A predominant loss of acid gastric juice, as in pyloric obstruction, leads to dehydration with alkalosis; a loss particularly of alkaline upper intestinal secretions, or strongly alkaline biliary and pancreatic secretions, leads to dehydration with acidosis. The accumulation of abnormal acids in the body, such as the ketone bodies, also leads to acidosis. The retention of sulphate, phosphate, and the radicles of organic acids with production of acidosis is a common event in renal disease. It also occurs in the advanced stage of dehydration as the result of impairment of renal function due to reduced volume-flow of blood through the kidney.

In estimating the state of dehydration in a patient, a great deal can be learned from simple, direct observations. The facial appearance of the patient, the degree of thirst, the dryness of the buccal mucosa and tongue, the turgidity of the skin and subcutaneous tissues are helpful. In examining the mucous membranes of the mouth the condition of the mucosa inside the upper and lower lips, which are less readily dried out by mouth breathing, is significant. Further evidence easily obtained and of much importance is the quantity and nature of the urine excreted during twenty-four hours. In the absence of diabetes insipidus or diabetes mellitus and severe nephritis, a daily output of over 1500 cc. urine is strongly presumptive, but

not infallible evidence that dehydration is not present. In addition, the specific gravity of the urine is important and if the specific gravity is below 1.015, as pointed out by Coller and Maddock, dehydration is not likely to be present (except in specific disease of the kidney).

Information pointing to the existence of dehydration is obtained if the clinical signs of alkalosis or acidosis are present, for, although dehydration may occur without disturbance of acid-base equilibrium, severe acidosis or alkalosis always implies dehydration. The deep forceful breathing of acidosis or the shallow breathing, increased muscular irritability, tremors and cramps of alkalosis or the strong odor of acetone on the breath, all indicate the need for specific fluid therapy.

Indirect evidence concerning the state of hydration of the body can be obtained by measuring during the twenty-four hour period the total amount of fluid taken into the body, and balancing this against the fluids lost, whether through urine, stool or vomitus.

Blood chemistry determinations may provide both direct and indirect evidence of body fluid concentration. In the early stage of dehydration when the loss is at the expense of interstitial and intracellular fluids no direct evidence can be obtained by chemical examination of the plasma. In the advanced stage of dehydration, the volume of the blood plasma is reduced, and this is indicated by an increase in the concentration of nondiffusible elements in the blood, namely, plasma proteins, red blood cells and hemoglobin. Also in severe dehydration, there is, as has been mentioned, impairment of renal function. In the presence of circumstances tending to cause dehydration, elevation of blood urea nitrogen above 30 mg. per cent or of nonprotein nitrogen above 40 mg. per cent is evidence of dehydration of advanced degree. Changes in plasma bicarbonate and plasma chloride from their normal values may be taken as indirect evidence of dehydration, inasmuch as these changes are commonly caused by the same processes which produce dehydration. Moreover, these changes in bicarbonate and chloride begin in the early stage of dehydration and are for this reason very useful evidence.

Summary of blood plasma values in dehydration:

Sodium—normal, 140-144 milliequivalents per liter.
In spite of the progressive loss of sodium from the body in dehydration, the parallel loss of water tends to keep the concentration of sodium in the plasma nearly normal, so long as renal function is accurate. With the development of impaired renal control in advanced dehydration, values either above or below the normal may be found. A relative increase in sodium concentration as compared with chloride means alkalosis, a relative decrease, in acidosis, provided there is not an accumulation in the plasma of other acid substances such as organic acids, phosphate and sulphate.

Chloride—normal, 100-106 milliequivalents per liter.
The direction of change in the chloride value depends on the underlying process causing the dehydration. If the major cause is continued loss of gastric secretions, very extensive reduction in chloride may be found. In the presence of other causes of dehydration, chloride may be found at its usual value or somewhat elevated. Reduction of chloride, as compared with sodium, usually indicates alkalosis and an increase acidosis.

Bicarbonate (CO_2)—normal, 24-28 milliequivalents per liter (55-65 vol. per cent).
Bicarbonate change is always secondary to change in other plasma factors, especially to alteration in concentration of sodium and chloride. As noted above, increase in sodium tends to cause increase in bicarbonate, and reduction of sodium a fall in bicarbonate. Chloride change causes an inverse change in bicarbonate, reduction causing increase in bicarbonate and extension decrease.

N. P. N.—normal, 20-30 mg. per cent.
In severe dehydration, retention of nonprotein nitrogen develops as a consequence of impairment of renal function caused by reduction of volume flow of blood through the kidney.

Plasma protein—normal, 6.5-7.5 Gm. per cent.
A rise in concentration of the plasma proteins is found in advanced dehydration and indicates a reduction of blood plasma volume.

Plasma volume—normal, 50 cc. per kg. of body weight.
Reduction of blood plasma volume is an eventual result of the process of dehydration. The presence of a decreased value for plasma volume indicates that interstitial and intracellular fluid reserves have been exhausted and that an advanced and dangerous degree of dehydration has been reached.

In treating dehydration, each case is an individual problem and rule-of-thumb procedure is undesirable. Certain general ideas are acceptable, however, and the most immediate concern is the function of the kidney. If anuria or oliguria is present renal excretion should be stimulated so that the kidney may eliminate accumulated catabolic substances and any excess of acid or base, and for this purpose 5 per cent glucose solution in distilled water given intravenously is useful. At the same time physiological salt solution may be given by hypodermoclysis.

Usually the acidosis or alkalosis of dehydration responds to the same treatment. The essential elements of sodium, chloride and water the kidney retains in quantity and proportion as needed, once renal function is active. At times, however, acidosis or alkalosis may be so severe, that corrective fluids must be given specifically with acidosis or alkalosis in mind. Ordinarily, the flow of urine should first be started by the intravenous infusion of 5 per cent glucose solution. Acidosis may then be treated by the intravenous administration of 5 per cent sodium bicarbonate solution, or by the intravenous or interstitial injection of 1.8 per cent sodium lac-

TABLE 1

The following table illustrates the types of fluid which meet the various needs in fluid therapy. The dosage recommended is only approximate, and obviously must vary widely with the individual case. These fluids have been found satisfactory in covering all the needs in fluid therapy arising in the care of patients on the Surgical Services of the Massachusetts General Hospital.

Fluid	Nature	Method of Administration	Indications	Dosage First 24 Hours per Kilogram Body Weight
0.9% sodium chloride (Physiological salt solution)	Isotonic, neutral reaction, in vivo yields relative excess of chloride	Proctoclysis Hypodermoclysis Intravenous infusion	Dehydration with or without Alkalosis or acidosis	50-100 cc.
5% glucose solution	Isotonic, neutral reaction, in vivo yields free water	Proctoclysis Hypodermoclysis Intravenous infusion	Oliguria of dehydration Ketosis Carbohydrate-lack	40-80 cc.
5% glucose solution with 0.9% sodium chloride	Hypertonic, neutral reaction	Intravenous infusion	Dehydration Ketosis	50-100 cc.
10% glucose solution	Hypertonic, neutral reaction	Intravenous infusion	Ketosis, severe Carbohydrate-lack	20-40 cc.
50% sucrose solution	Hypertonic, neutral reaction	Intravenous infusion	Increased intracranial pressure	5-10 cc.
5% sodium bicarbonate solution	Hypertonic, alkaline	Intravenous infusion	Severe acidosis, supplementary to 0.9%NaCl	5-10 cc.
1.8% sodium lactate solution	Isotonic, neutral in vitro, produces alkali in vivo	Hypodermoclysis Intravenous infusion	Severe acidosis, supplementary to 0.9%NaCl	10-20 cc.
6% acacia in 0.9% sodium chloride	Isotonic, osmotic pressure of colloids similar to that of plasma proteins	Intravenous infusion	Shock and hemorrhage (Temporary substitute for transfusion)	10-20 cc.
Blood, whole or with 0.25% sodium citrate		Intravenous infusion	Hemorrhage Shock Chronic anemia Deficient plasma proteins Acute and chronic infections Hemorrhagic disease	10-20 cc.

tate solution. It is to be borne in mind that the administration of such alkaline fluids is only a part of the treatment of dehydration with acidosis, and is to be followed by physiological sodium chloride solution. Sodium bicarbonate and sodium lactate solutions may combat acidosis but they cannot repair dehydration, since they do not contain the essential chloride ion in addition to sodium. Alkalosis may ordinarily be treated in the presence of active renal function by the administration of physiological salt solution, for this solution, compared with the plasma, actually contains an excess of the acid chloride.

In determining the amount of fluid to be given daily in treating dehydration we are guided by the general condition and appearance of the patient, the age and weight of the patient, the balance of intake and output, the quantity and specific gravity of the urine and repeated blood chemistry determinations. As a rule the daily intake of fluid in an adult should exceed the measurable output by at least 2000 cc., for an average loss of two liters a day takes place insensibly through skin and lungs. If perspiration is excessive, this loss is much increased. The fluid intake should be sufficient to permit the urine volume to be at least 1500 cc. per day in the adult. Should a patient become edematous during restorative fluid therapy, less fluid should be given and 5 per cent glucose instead of physiological salt solution is indicated.

Conditions requiring blood transfusion. Concerning the rather special indications for fluid therapy as seen in the need for transfusion of blood, little will be said in this paper. In conditions of acutely reduced blood volume such as hemorrhage and shock, blood transfusion is specific treatment. Other conditions in which blood transfusion may be of benefit, such as severe burns, deficiency of plasma proteins, hypochromic anemia, sepsis and hemorrhagic tendency are rather apart from the scope of the present discussion.

Hypertonic fluid therapy. This phase of fluid therapy requires brief discussion. The hypertonic solutions used, such as 25 or 50 per cent glucose, 20 per cent sodium chloride or 50 per cent sucrose, must be given carefully by vein. These solutions are highly irritating to the tissues and readily produce sloughing if injected outside the wall of the vein. Veins frequently become thrombosed at the site of injection of such fluids. Of these solutions, 50 per cent sucrose is probably the best. Sucrose when given by vein is a nontoxic substance which does not enter the tissue cells and is excreted quantitatively in the urine, along with much water from the tissues. This solution of sucrose possesses a great advantage over hypertonic glucose solution in that intracranial pressure is reduced with much less tendency for a secondary rise to occur. A 50 per cent solution of sucrose may be given intravenously to the extent of 5 cc. per kilogram of body weight in the adult, at the rate of 10 cc. per minute.

The chief field of usefulness of hypertonic intravenous therapy is seen in conditions of increased intracranial pressure following trauma to the skull, as in depressed fracture and injury to the brain substance.

Summary: A critical discussion of fluid therapy as concerns surgical practice is presented, dealing with the following considerations:

1. Basic physiological factors.
2. Appropriate methods.
3. Types of fluid to be used.
4. Indications for the use of fluid therapy, with particular emphasis on treatment of dehydration.

A tabulation of pertinent material is contained in table 1.

ACUTE APPENDICITIS AND MEASLES*

BY HENRY W. HUDSON, JR., M.D.,† AND CECIL KRAKOWER, M.D.†

DURING a five-year period one of us (H. W. H., Jr.) has observed eight cases of acute appendicitis during the course of measles. This unique experience has led us to review the literature and to record our own findings, in order that attention may be called to a curious clinical picture.

In 1901 Williams[1] reported the case of a boy of twelve years who, on the day following the appearance of a measles rash, developed signs of acute appendicitis. He was successfully operated on. The pathologic report by Mallory was that of acute inflammation with a concretion and pus within the lumen of the appendix.

In 1928 Popper[2] reported the case of a man of twenty-six years with signs of acute appendicitis and a white blood cell count of 7,000. Under the operating room lights a measles rash was visible. At operation a thickened, reddened, appendix was removed. There was turbid fluid in the iliac fossa. The day following, typical measles was present.

In the same year Fischer[3] from his personal

*From the Departments of Surgery and Pathology, Children's Hospital, Boston.

†Hudson, Henry W., Jr.—Associate Surgeon, Children's Hospital. Krakower, Cecil—Acting Pathologist, Children's Hospital, 1935-1936. For records and addresses of authors see "This Week's Issue," page 97.

experience reported the association of measles and appendicitis in three of 3,000 "young persons and children" with appendicitis. He described a girl of fifteen years who was operated on the day before the rash appeared and a fourteen year old girl who was operated on after two days of abdominal cramps and vomiting. The latter had a white blood cell count of 5,000 and, at operation, presented a gangrenous appendix with peritonitis. Four days after operation a morbilliform rash appeared. His third patient, a boy of seventeen years, developed right-sided pneumonia two days after the eruption had appeared. Two days later signs of appendicitis were present but were considered to be due to the pneumonia. Two days later, six days after the exanthem, there were signs of spreading peritonitis. At operation there was generalized peritonitis of appendiceal origin. All three patients recovered, two after stormy convalescence.

Rost[4] believed that the association of measles and appendicitis was rare. He reported a case of a four year old boy who developed signs of appendicitis five days after the onset of measles and while the rash was evident. This patient was observed until the twelfth day of illness when an appendiceal abscess was drained. Rost made inquiries of various pediatrists and surgeons in Germany and, although he did not state the number of cases collected, concluded that the occurrence of appendicitis during the course of measles was more than a coincidence. He felt that gangrene was apt to occur rapidly and that it was safe to operate during measles.

Trepel,[5] writing on the surgical complications of measles, cited Popper, Fischer and Rost and two cases reported by Gottstein and Kutner and by Ambuhl. She added nine cases observed between 1921 and 1930 and two more in 1931 that were thought to have pneumococcic peritonitis until autopsy revealed the peritonitis to be due to rupture of the appendix. Of her cases, five developed appendicitis during the prodromal stage, one during the eruption and five during convalescence. The clinical course in those cases occurring during the prodromal stage was the more acute and fulminating. She emphasized that to delay operation was unwise.

There were five reports dealing with the subject in 1932. Ferru, Perdoux and Michiels[6] described a boy of five years with fever and vomiting on May 30 and a measles rash on June 3 together with abdominal pain, vomiting and flexion of the right thigh. On June 6 there were signs of pneumonia and on June 8 of appendicitis. On June 11 an appendiceal abscess was drained and recovery followed. Herzberg[7] and Finkeldey[8] individually reported a case of appendicitis developing during the prodromal stage of measles and commented on the presence of giant cells in the lymphoid tissue and mucosa of the appendix. Thenebe, Hirshberg and Ceneí[9] reported six instances of appendicitis in 372 consecutive admissions for measles to the Hartford Isolation Hospital. In one patient appendectomy was performed during the prodromal stage (two days before the rash) and in three during the eruption stage (six, five and sixteen days after the onset of illness). These authors advanced the theory that lymphoid hyperplasia in the submucosa of the appendix might, through swelling, bring about ischemia with resulting necrosis and inflammation. These cases were observed during a ten-year period and the authors inclined to the belief that the association was coincidental. All the patients recovered. Davidsohn and Mora[10] reported four cases, two during the prodromal stage, one on the second day of eruption and one during convalescence. Giant cells were found in the mucosa and submucosa in the appendices of the two in the prodromal stage.

In 1935 Hathaway[11] reported a case with autopsy findings of a child of two and a half years with peritonitis secondary to a perforated suppurative appendicitis occurring in the prodromal period.

CASE REPORTS

1. D. S. No. 146,439, male, aged seven.

This patient was admitted to the Children's Hospital on February 20, 1931. On February 9 he had complained of headache. He coughed and his eyes were "watery". He felt ill and had fever and photophobia. On February 14 a characteristic measles rash appeared. That day he complained of soreness and pain in the right side of the chest and abdomen. The pain was intermittent, aggravated by cough but not by deep breathing. The pain was dull and persistent.

On admission the child was acutely ill and complained of abdominal distress. He lay in bed with thighs flexed. The skin showed pigmentation from the recent measles. The abdomen was full and resistant, particularly on the right. There was tenderness in the right lower quadrant extending well into the flank where there was a rounded, tender mass between the twelfth rib and the crest of the ileum.

On February 22 a large abscess was drained extraperitoneally. Though obviously of appendiceal origin, the appendix was not palpable within the abscess cavity.

Following operation the temperature became normal and convalescence was rapid. He was discharged March 12 and readmitted May 15 for appendectomy. He was discharged May 25. The appendix was not examined histologically.

Diagnosis—Appendiceal abscess.
Measles, convalescent.

2. E. W. No. 147,869, female, aged seven years, ten months.

This girl entered the Children's Hospital April 16, 1931, thirteen days after the onset of illness characterized by a chill and fever. Two days later measles was recognized. Coincident with the appearance of the rash she complained of pain in the right side of the abdomen aggravated by lying on that

side. The pain persisted and at times was referred to the epigastrium. Nine days before admission she vomited twice after meals. She ran a fever varying between 101° and 102°. Two days before admission there was anorexia and nausea and, on one occasion, vomiting. The day before entry to the hospital the pain was more severe.

When admitted she was alert, bright and appeared acutely ill. The temperature was 100°; the pulse rate 126 and the respirations 25. She lay in bed with thighs flexed. There was slight abdominal distention with marked tenderness in the right lower quadrant which was accompanied by muscle spasm. A mass about 10 cm. in diameter occupied the right lower quadrant and suprapubic region. A tender mass was palpable by rectum on the right side of the pelvis.

Operation revealed an abscess which had eroded through the transversalis muscle. A large amount of pus and a thin-walled, blue, necrotic, glove-finger shaped mass was removed. The mass was thought to represent the distal half of the appendix. There was a fecolith about 1 inch long free in the abscess cavity. The appendix stump could not be found.

The temperature abated and convalescence was gratifying. She was discharged May 9.

From the abscess cavity a colon bacillus, a pneumococcus and a poorly growing, slightly hemolytic staphylococcus were cultured.

Fourteen months later she was readmitted for repair of an incisional hernia. The appendix was sought for and removed. It appeared intact and not abnormal. Recovery was uneventful.

Pathologic report: (S-33-364)

The appendix was not remarkable in gross examination. Histologically the mucosa was intact with increased numbers of eosinophiles. There was abundant lymphoid tissue with some depletion of the secondary centers and replacement by reticular cells. There was slight scarring of the inner circular muscular coat with perivascular lymphocytic infiltration in the serosa and proliferative endarterial changes in several mesenteric arteries.

Diagnosis—Appendiceal abscess.
Measles, convalescent.

3. D. B. No. 170,224, female, aged six years, one month.

This girl was admitted to the Children's Hospital April 21, 1933, four days after the onset of illness characterized by fever, cough and conjunctivitis. Koplik spots were recognized by the mother, formerly a nurse. The day before admission a measles exanthem appeared. Thirty-six hours before admission and just before the rash was noted, she awakened at night complaining of sharp pain in the right lower quadrant. This was followed by vomiting. An enema was returned with fecal contents, following which the child slept. The day before admission abdominal pain continued. The temperature was 103°.

On admission the temperature was 101, the pulse rate 155 and the respiratory rate 38. She appeared acutely ill and presented a typical measles rash. The abdomen was diffusely tender, particularly in the right lower quadrant where there was muscle spasm and an ill-defined mass.

At operation the peritoneum was injected and edematous. When incised the inflamed omentum presented, and "soapy" exudate welled up from the right iliac fossa. The appendix, enveloped in inflamed omentum, was removed. Draining was instituted.

Convalescence was rapid.

Pathologic report: (S-33-170)

The appendix was wrapped in omentum, enclosing an abscess containing 2-3 cc. of foul-smelling pus. The external omental surface was deep red in color and covered in areas by fibrinopurulent exudate. In the proximal portions of the appendiceal lumen there was a soft fecolith measuring 1.5 cm. in length. The distal portion was distended by slightly hemorrhagic purulent exudate. The mucosa was diffusely ulcerated and of dirty reddish-gray appearance. Serial sections from a number of blocks were studied microscopically. There was an acute diffuse phlegmonous inflammation irregularly involving all coats with fairly extensive ulceration. The lymphoid tissue was considerably depleted even in nonulcerated areas. In the latter there were many plasma cells in the mucosa and in the lymphoid tissue and lymphatics of the submucosa. Together with these there were fairly frequent large cells, seemingly variants of plasma cells or of monocytes with basophilic cytoplasm; large nuclei with well-defined nuclear borders and irregular chromatin threads with occasional thickenings which were not at all confined to the periphery. Cells of this type were not infrequently found in mitosis and occasionally were lobulated, bi- or trinucleated. In one small submucosal lymphatic there was one cell of this type with a clustered group of about 8-10 nuclei similar to the giant cells described in the literature. These cells were better defined in sections stained by hematoxylin-eosin than in those by eosin-methylene blue or Giemsa.

Diagnosis—Acute suppurative appendicitis with periappendiceal abscess.
Measles.

4. J. McM., male, aged nine years.

This boy was seen in consultation at the Framingham Union Hospital on March 4 and operated on March 5, 1934. He became ill on February 12 and a typical measles rash was apparent February 16. On February 20 he complained of generalized abdominal discomfort and vomited several times. The pain persisted. There was diarrhea February 20 and 24 and generalized abdominal tenderness. He then improved and fever, which had been present, abated. On March 2 the temperature became elevated, the child appeared quite ill and he complained of right-sided abdominal pain. On March 4 the temperature was 103°, the pulse rate 120. He was flushed. The tongue, buccal mucous membranes and fauces were very red. He coughed frequently and breath sounds were suppressed at the base of the right lung. There was tenderness and muscle spasm limited to the right flank and right lateral aspect of the abdomen. Maximum tenderness was obtained at McBurney's point. There was tenderness and edema of the rectal wall high on the right.

Operation was performed March 5. The peritoneum was red and edematous. There was no free exudate but posteriorly and laterally to the cecum there was a large abscess extending into the flank and toward, but not into, the pelvis. The pus had a feculent odor. The appendix was not palpable.

Following drainage of the abscess, recovery was prompt. Readmission for appendectomy was advised, but the advice was not followed.

Diagnosis—Appendiceal abscess.
Measles, convalescent.

5. L. M., male, aged seven years.

This boy was seen in consultation March 29, 1934 and operated on in the Framingham Union Hospital on March 31.

On March 19 he developed fever of 105, vomiting

and diarrhea. Vomiting was limited to the first day of illness but diarrhea with mucus, but no blood, persisted as did the fever. On March 21 a measles rash was recognized. On March 24 he complained of abdominal pain. During the next five days there was recurrent abdominal distention, partially relieved by the use of a rectal tube, abdominal pain and fever varying between 99 and 101.

When examined March 29, he appeared acutely but not critically ill. He complained bitterly of paroxysmal pain across the lower abdomen. The temperature was 102, the pulse rate 138. The tongue was dry and coated. There was a well-defined suprapubic mass about 4 inches in diameter extending slightly more to the left than to the right. There was muscle spasm adjacent to the mass. A large, very tender mass was palpable through the rectum.

At operation, March 31, a tremendous abscess containing 300 or 400 cc. of foul pus was drained. The abscess was confined to the left suprapubic region and pelvis. The appendix was not found, but a bit of necrotic material resembling the appendix was discharged.

Convalescence was protracted and a small sinus drained intermittently for six months. Appendectomy was refused.

Diagnosis—Appendiceal abscess.
Measles, convalescent.

6. R. B., No. 174,959, female, aged five years, six months.

This child was admitted to the Children's Hospital May 13, 1934, one week after the onset of illness characterized by fever, cough and conjunctivitis. On May 10 measles exanthem was present and she vomited three times, each time after a paroxysm of coughing. She did not complain of pain and slept well. The day before admission she seemed quite well, coughed a little, but slept most of the time. In the midafternoon she complained of midabdominal soreness, was nauseated and vomited once. She slept the early part of the night, but wakened at 2:00 a. m. complaining of right-sided abdominal pain. She was feverish. She was seen in consultation the following afternoon and sent to the hospital for operation.

The temperature was 101, the pulse 110, the respirations 50. The child appeared acutely ill and coughed frequently. There was a fading measles exanthem. Diffuse crackling râles were present throughout both lungs, more marked on the right, where an area of dulness was present below the scapula. There was marked tenderness and muscle spasm throughout the right side of the abdomen, more particularly in the lower quadrant. There was tenderness on the right during rectal examination.

At operation on May 13, the peritoneum did not appear inflamed, but when incised the omentum presented overlying the cecum. Behind the cecum a lemon-sized abscess cavity containing foul pus and a swollen, necrotic appendix perforated near the base was encountered. A fecolith was extending through the perforation. The appendix was removed and drainage instituted.

Convalescence was gratifying and the child was discharged thirteen days after operation.

Pathologic report: (S-34-195)

Grossly the appendix was greatly swollen, with a plaque of fibrinous exudate over one area of the reddened serosa. There were two fecoliths within the lumen of the appendix, one at the very distal end. The mucosa was edematous and deeply reddened. Serial sections were cut and stained from a number of blocks. In all there was an acute diffuse phlegmonous and suppurative inflammation involving all coats, with irregular and extensive mucosal ulceration, lymphoid depletion and very little reticular cell proliferation. In some of the sections, especially those from nonulcerated mucosal portions, there were frequent plasma cells in an edematous, loose and vascular mucosal and submucosal stroma with fairly frequent but fewer cells of the type described in case 3.

Diagnosis—Acute suppurative appendicitis with perforation and abscess formation.
Bronchopneumonia.
Measles, convalescent.

7. R. P., No. 199,921, female, aged eight years, nine months.

This child vomited at breakfast March 14, 1936. During the morning she vomited several more times. She did not complain of pain. Her temperature was normal. At 1:30 p. m. she was examined by her physician who found a mouth temperature of 99, a slightly inflamed throat and slight inflammation of one ear drum. She vomited several times in the early afternoon, then fell asleep, and awakened at 4:30 complaining of abdominal pain. At 6:30 p. m. the temperature was 102 and there was tenderness and muscle spasm in the right lower quadrant of the abdomen. Rectal examination was painful.

She was admitted to the Children's Hospital and operation was performed at 9:00 p. m. A swollen, tense, deeply red appendix was removed. The lumen contained pus under tension.

On the second day after operation the temperature rose to 101.8 and there was infrequent cough. She complained of headache and photophobia. She slept well. On the third day Koplik spots and a faint rash were noted. On the fourth and fifth days a well-marked measles exanthem was present. On the sixth day the rash had faded, the conjunctivitis had disappeared and the temperature was 100. The wound healed well. She was discharged on the eleventh day after operation.

Pathologic report: (S-36-104)

There was mild to moderate acute diffuse inflammation involving all coats with mucosal ulceration. There was one giant cell in the mucosa of only one section in serials from several blocks.

Diagnosis—Appendicitis, acute.
Measles.

8. H. S., No. 143,597, male, aged six years.

This boy became ill April 1, 1936 and developed typical measles with rash on April 4. He was not very ill. On April 5 and 6 he was considered essentially well. At 1:30 a. m. April 7 he awakened from sleep with severe abdominal pain. He vomited three times. Between 1:30 a. m. and 9:30 a. m. he had frequent attacks of severe, paroxysmal abdominal pain. He slept from 9:30 to 10:30 a. m., when he had another colicky attack of pain. There was further pain at 11:30 a. m. Examination revealed the patient to be acutely but not critically ill and in no apparent distress. He stated that he had pain and pointed to McBurney's area. His temperature was 98.8, the pulse rate 64. His tongue was dry and coated. There was pigmentation as a result of the measles rash. The abdominal examination was entirely negative. On rectal examination, however, there was a point of exquisite tenderness very high on the right. The white blood count was 11,300 and the differential count normal. The urine was negative on examination.

He was admitted to the Children's Hospital on April 7 and operation was performed. When the peritoneum was incised, slightly cloudy odorless fluid welled up. This was cultured. An abundant

growth of the Bargen-Logan bacillus in pure culture was obtained in eighteen hours. A normal appearing, but very long, appendix was removed. The terminal ileum was inspected. It was not inflamed. There was no diverticulum. The mesenteric lymph nodes were rather prominent, but not red or succulent. One node was removed for examination. The wound was closed.

Convalescence was rapid and afebrile. He was discharged nine days after operation.

Pathologic report: (S-36-135)

Except for mild vascular congestion, the appendix grossly was not remarkable. Serial sections from a number of blocks of tissue were studied microscopically. There was an early acute inflammation chiefly involving a narrow sector of muscular and serosal coat, in only one block, characterized by vascular dilatation, leukostasis, endothelial swelling and perivascular leukocytic infiltration. In most blocks there were well-defined areas of mucosal edema and in instances submucosal vascular changes similar to those in the muscular and serosal coats but with little perivascular leukocytic infiltration. The lymph node was characterized by widened sinusoids with many lymphocytes and few monocytes. There were rare polymorphonuclears.

Diagnosis—Early mild acute appendicitis.
Early mild peritonitis.
Measles, convalescent.

DISCUSSION

Analysis of the cases reported above brings out the fact that the symptoms and signs pointing to appendicitis bear a close time relationship to the prodromal and eruption stages of measles. Thus, in cases 1, 2 and 3, the appearance of the exanthem and a complaint of abdominal pain were noted on the same day. In case 7, acute appendicitis occurred on the first day of illness and three days before the rash was noted. In the remaining cases, 4, 5, 6 and 8, the onset of abdominal symptoms was four, two, four and seven days, respectively, after the eruption was noted. In two of these four the clinical histories were less reliable than in the others and it is at least possible that the onset of appendiceal inflammation coincided more closely with the rash than appears from the records.

In another patient, not seen but of whom we have personal knowledge, abdominal symptoms and signs were present the day before the rash, but as Koplik spots, leucopenia and cough were noted, operation was deferred. The day following hospital admission, a measles rash was present. Two days later there were signs of peritonitis, and operation was performed. Pneumonia developed four days after operation and death ensued. Necropsy revealed a generalized peritonitis (*B. coli*), secondary to a perforated appendix. The appendix histologically presented acute and chronic inflammatory changes. There were no giant cells. There were occasional groups of monocytes of the type described in the case reports. No giant cells were seen in the lymph nodes, spleen or other portions of the gastrointestinal tract.*

There is very little known about the visceral lesions of measles. This has been due to the infrequency with which surgical and autopsy material can be obtained during the course of the disease. The character of the lesions in the sequelae, however, has been fully described (post-measles pneumonia, encephalitis). It would be fairly easy to explain the onset of appendicitis, particularly in the prodromal and early exanthematic stages, if visceral lesions comparable with those of the skin or buccal mucous membrane occurred, as they would allow for the ready ingress of secondary invaders. One might also expect a higher incidence of such complications in that instance. But as yet no such visceral lesions have been described in the human being, although they are said to occur in experimental animals. The presence of giant cells in lymphoid organs, of which there are nine reports in the literature,† although of diagnostic significance, may merely indicate that there are possibly certain tissue changes (functional or immunological) which in one or another way may predispose to infection. Their presence and relationship to inflammatory processes appear to be very inconstant, however. Whereas, Herzberg, Finkeldey and Davidsohn and Mora have described them in acute inflammatory appendices, von Schultze[12] and Fischer[13] have described them in the same organ in the prodromal stages of measles without any inflammatory changes. Their absence or scarcity has been explained on the basis that these large multinucleated cells rapidly degenerate and disappear, particularly in the presence of infection. Thus, in Hathaway's case giant cells were found in the peribronchial, retroperitoneal and peripancreatic lymph nodes, but were absent in the lymphoid tissues of the gastrointestinal tract, including the appendix and mesenteric nodes. Yet, in one instance we could find no giant cells in a relatively normal appendix removed during the prodromal period, although serial sections of several blocks were examined.‡ We could find only one giant cell of the type described in the literature in the one instance (case 3) where the appendix was removed one day after the appearance of the rash and one in the appendix removed three days before the appearance of the exanthem (case 7).

It was thought, however, that a careful comparison of the sections obtained from the cases with acute appendicitis during the course of measles with some 200 from children where

*Another patient not seen, but described to me by a health official in 1934, presented measles and appendicitis and died. The relation of appendicitis to the rash is not known.

†In addition to those mentioned here in connection with the appendix there have been three reports by Alagna,[14] Warthin[15] and Finkeldey,[16] in which giant cells have been found in the tonsils during measles.

‡This case not referred to elsewhere.

there was no such relationship, might reveal some differences to help explain the fairly strict temporal association of the two. Although it was realized that similar factors to those ordinarily underlying appendicitis (fecoliths, pharyngitis and tonsillitis) were present at least two significant differences were found. In general there was less lymphoid tissue with practically no secondary centers or germinal follicles in the group with measles. In the control group, the germinal follicles were generally large and prominent. There appeared to be more plasma cells, particularly in the submucosa, in those with measles and in two (first day after exanthem and less so on the third day after exanthem) there were numbers of larger cells in the mucosa, lymphoid tissue and submucosa with basophilic cytoplasm and large prominent nuclei which were often oval or spherical and, at times, lobated and distorted, occasionally with two and rarely with three nuclei. Such cells were infrequently observed in the mucosa of the controls and rarely in the submucosa and lymphoid tissue. The distribution and character of the inflammatory exudate did not differ in the two groups. No specific vascular lesions were found. The proliferation of reticular cells was equally prominent or less conspicuous in the two groups.

It is of course realized that the histologic material is too meager to warrant broad conclusions. Nevertheless there seems to be some anatomic variation in the two groups which lends support to the clinical impression that the association of measles and appendicitis is more than merely coincidental.

Five patients seen and operated on thirteen days, thirteen days, twenty-one days, twelve days and seven days, respectively, after the onset of illness had well-localized appendiceal abscesses. One operated on the day following the rash and the fourth day of illness presented an acutely inflamed appendix, wrapped in omentum with localized peritonitis. All recovered and, in all, the symptoms and signs of appendicitis were masked by the stigmata of measles. These two facts suggest a less virulent infection than is often the case in childhood appendicitis.

Adding the eight personal cases, the additional one known from personal communication and those reported in the literature, there are forty cases. In fifteen, appendicitis developed during the prodromal stage, in twelve during the eruptive stage and in thirteen during the immediate convalescent period. Thirty-nine of the forty patients were children or adolescents. There were only two deaths.

CONCLUSIONS

To the thirty-one instances of measles and appendicitis reported in the literature nine are added. From this experience and the review of the literature, the conclusion is reached that there is an intimate relationship between the two diseases.

Regardless of whether measles is an etiologic factor in the development of appendicitis, it is established that the two may coexist.

In the presence of measles a thorough abdominal examination is indicated, together with careful appraisal of the symptoms of abdominal pain and vomiting which are frequently present.

If the signs of appendicitis are demonstrated, operation is indicated despite the presence of measles.

REFERENCES

1. Williams, H.: A case of measles complicated by appendicitis. Boston M. & S. J. **144**:642 (June 27) 1901.
2. Popper, H. L.: Appendicitis und Masern. Med. Klin. **24**:493 (March 30) 1928.
3. Fischer, A.: Appendicitis und Masern. Zentralbl. f. Chir. **55**:1545 (June 23) 1928.
4. Rost, F.: Über Appendicitis bei Masern. Zentralbl. f. Chir. **55**:905 (April 14) 1928.
5. Trepel, G.: Chirurgische Komplikationen bei Masern. Monatschr. f. Kinder. **54**:1, 1932.
6. Ferru, Perdoux, and Michiels: Appendicite suppurée au cours d'une rougeole compliquée de broncho-pneumonie chez un enfant. Bull. Soc. de pediat. de Paris. **30**:203 (Aug.) 1932.
7. Herzberg, M.: Giant cells in lymphoid tissue of appendix in prodromal stage of measles; report of isolated case. J. A. M. A. **98**:139 (Jan. 9) 1932.
8. Finkeldey, W.: Riesenzellbefunde bei akuter Wurmfortsatzentzündung. Ein Beitrag zur Histopathologie der Veränderungen des Wurmfortsatzes in Maserninkubationsstadium. Virchows Arch. f. Path. Anat. **284**:518, 1932.
9. Thenebe, C. L.; Hirshberg, M., and Cenci, V.: Acute appendicitis as complication of measles; report of 6 cases. Arch. Pediat. **50**:28 (Jan.) 1933.
10. Davidsohn, I., and Mora, J. M.: Appendicitis in measles. Arch. Path. **14**:757 (Dec.) 1932.
11. Hathaway, B. M.: Generalized dissemination of giant cells in lymphoid tissue in prodromal stage of measles. Arch. Path. **19**:819 (June) 1935.
12. von Schultze, W. H.: Der Wurmfortsatz im Prodromal-Stadium der Masern. Munchen. med. Wchnschr. **80**:576 (April 14) 1933.
13. Fischer, W.: Uber die Diagnose der Masern im Prodromalstadium Eigenartige Befunde am lymphatischen Apparat der Appendix. Beitr. z. path. Anat. u. z. allg. Path. **91**:474, 1933.
14. Alagna, G.: Histopathologische Veränderungen der Tonsille und der Schleimhaut der ersten Luftwege bei Masern. Arch. f. Laryngol. u. Rhinol. **25**:527, 1911.
15. Warthin, A. S.: Occurrence of numerous large giant cells in tonsils and pharyngeal mucosa in prodromal stage of measles; report of 4 cases. Arch. Path. **11**:864 (June) 1931.
16. Finkeldey, W.: Über Riesenzellbefunde in den Gaumenmandeln, zugleich ein Beitrag zur Histopathologie der Mandelveränderungen im Maserninkubationsstadium. Virchows Arch. f. path. Anat. **281**:323, 1931.

A SIMPLE METHOD OF OXYGEN ANALYSIS FOR USE IN OXYGEN TENT THERAPY*

BY JOSEPH E. F. RISEMAN, M.D.,‡ AND GERSON LESNICK, B.S.‡

THE patient within an oxygen tent may fail to receive an adequate supply of oxygen unless gas analyses are performed at frequent intervals. Barach[1] has recently called attention to this danger and experience at the Beth Israel Hospital is in complete accord with his views. Unfortunately the available methods of oxygen analysis are not adapted for use by the nurse or attendant in charge of the patient. While it is true that the methods of analysis "can be learned in one-half hour by almost any attentive individual"[1], from one to three persons must be instructed each time a tent is put into operation and few institutions are able to arrange for the necessary teaching staff.

The apparatus described below was devised to satisfy the need for an instrument which would be accurate, inexpensive and simple enough to operate so that it could be used efficiently without any previous instruction or experience. The accuracy of the method is shown in table 1. It is evident that the method is sufficiently accurate for clinical use. The cost of the materials used in making six analyzers at the Beth Israel Hospital was $22.54.† The apparatus can be built by anyone handy with tools. The simplicity of operation is attested by the fact that nurses and laymen without supervision and with no previous experience with oxygen analysis have encountered no difficulty in using the apparatus the first time.

TABLE 1

THE ACCURACY OF THE METHOD

Gas Sample Number	Per Cent Oxygen Content		
	Method of * Van Slyke and Sendroy[4]	Method Described in Text	
		Instrument A†	Instrument B†
1‡	20.70	21.0	20.5
2	31.51	31.0	32.0
3	43.62	43.5	43.0
4	55.04	55.5	55.0
5	70.69	71.0	70.0
6	78.88	80.0	80.5
7	88.59	88.0	88.5
8§	99.49	99.0	100.0

*Average of two analyses differing by 0.5 per cent or less.
†Average of two analyses differing by 2 per cent or less.
‡Room air.
§Sample direct from oxygen tank.

DESCRIPTION OF APPARATUS

The assembled apparatus is shown in figure 1. In principle the method consists of absorbing the oxygen from a known volume of gas and determining the residual volume. The oxygen is absorbed by means of copper gauze and an ammoniacal solution. Simplicity of operation is attained by three devices which result in automatic measuring of the volumes of the sample and the residual gas and in simplified operation of a three-way valve.

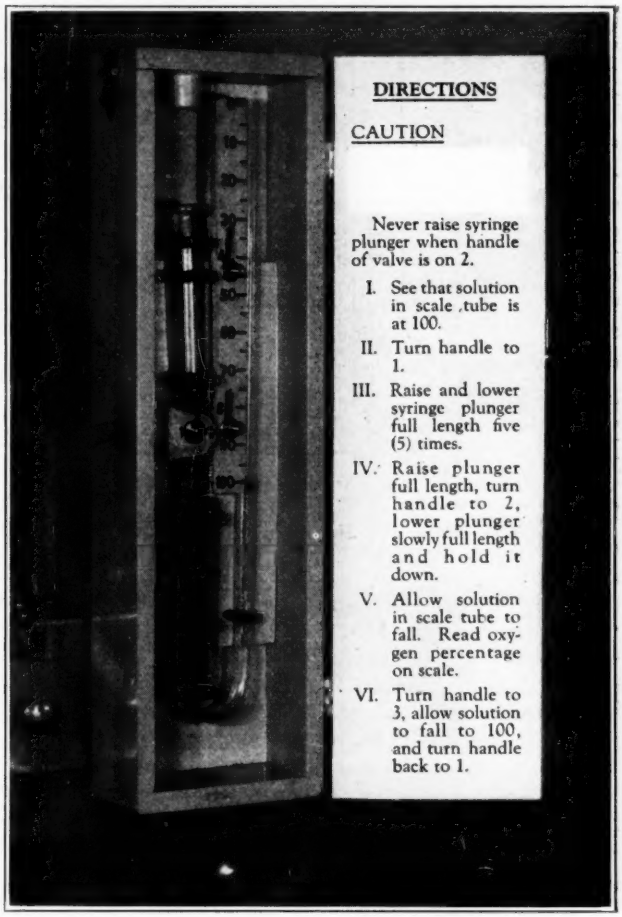

DIRECTIONS
CAUTION
Never raise syringe plunger when handle of valve is on 2.
I. See that solution in scale tube is at 100.
II. Turn handle to 1.
III. Raise and lower syringe plunger full length five (5) times.
IV. Raise plunger full length, turn handle to 2, lower plunger slowly full length and hold it down.
V. Allow solution in scale tube to fall. Read oxygen percentage on scale.
VI. Turn handle to 3, allow solution to fall to 100, and turn handle back to 1.

FIGURE 1. The apparatus assembled and mounted on the tent.

A stop built into the box (figs. 1 and 2) which contains the analyzing apparatus automatically limits the withdrawal of the plunger of a glass syringe (figs. 1 and 3) so that the sample of gas measures exactly 10 cc. This gas sample is passed into an absorption chamber. The fluid displaced rises in a calibrated side tube; as the oxygen is absorbed, this column

*From the Medical Research Department of the Beth Israel Hospital and the Department of Medicine of Harvard Medical School.

†These analyzers were made with brass stopcocks. A stainless steel valve is less likely to be corroded by the solutions used, but is more expensive.

‡Riseman, Joseph E. F.—Assistant in Medicine, Harvard University Medical School 1931-. Lesnick, Gerson. For records and addresses of authors see "This Week's Issue," page 97.

of fluids falls; the volume of the residual gas, and therefore the percentage of oxygen, is indicated automatically by the height of the column.

A three-way valve allows one to direct the flow of gas in the desired direction (figs. 1 and 3). The positions of the valve handle are numbered (figs. 1 and 4) so that the technician simply moves the handle in a clockwise direction from position 1 to position 2 and to position 3. Position 1 connects the measuring syringe with the tent, position 2 allows the gas sample to be passed into the absorption chamber, and position 3 resets the apparatus for the next analysis. Thus the nurse has no sample and residual volumes to measure, no fluid levels to adjust and no uncertainty as to which way the valve has been turned.

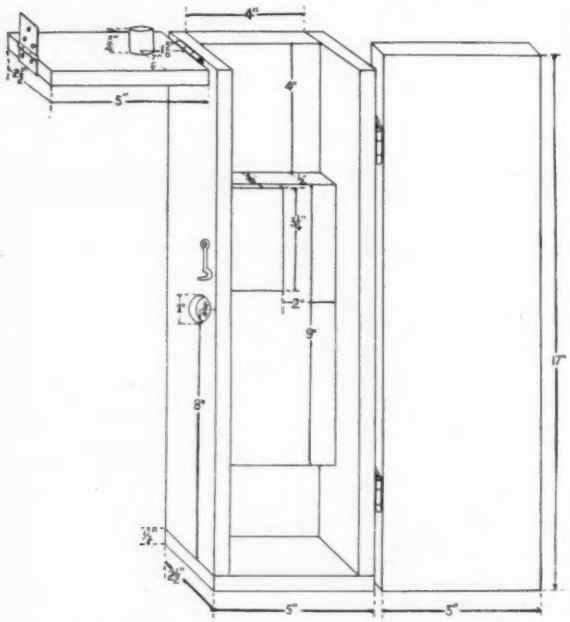


FIGURE 2. Container to protect glass parts and ensure automatic measuring of sample to be analyzed. To mount the analyzer first fasten the glass syringe and stopcock (see figure 1) so that when the top of the plunger rests against the dowel stop, the syringe will hold exactly 10 cc.

For high concentrations of oxygen (90 per cent-100 per cent), such as are used in the type of tent described by Fine and his co-workers,[2] an absorption chamber with a rounded or conical top (fig. 5) is necessary, but for ordinary clinical use (concentrations up to 85 per cent) the barrel of a large-tipped 30 cc. syringe is equally satisfactory, readily available, and inexpensive since it utilizes material frequently discarded when the plunger becomes broken.

Breakage is minimized by protecting the syringe tip with DeKhotinsky cement and by mounting the analyzer in a sturdy wooden box (figs. 1, 2, 3). The top of this box is fastened by hinges so arranged that release of a thumbscrew allows it to be thrown back to permit the removal of the syringe plunger for cleaning or lubrication (fig. 2).

The assembled apparatus is attached permanently to the oxygen tent (fig. 1), a separate analyzer being used for each tent. The side arm of the valve is connected to the hose carrying air *from* the tent by rubber tubing no larger than 1/8″ in diameter and 12″ in length.

Directions for use have been found to be self-explanatory. They are mounted permanently on the door of the box and covered with a piece of washed x-ray film. (See figure 1.)

CALIBRATION OF THE INSTRUMENT

The scale is marked on a wooden rod which partially covers the glass tube and is secured by thumbscrews permitting adjustment of the 100 mark (figs. 1 and 6).

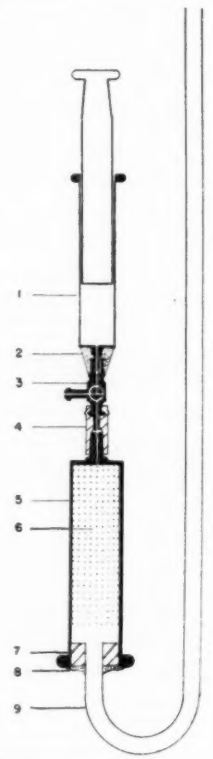


FIGURE 3. *The analyzer.*
1. 10 cc. glass syringe.
2. DeKhotinsky cement.
3. Three-way metal valve (preferably of stainless steel) with luer tip, luer adaptor and side arm for rubber tubing.
4. Rubber tubing, about 1 inch long with ⅛ inch bore and ⅛ inch wall.
5. The absorption chamber. A large-tipped 30 cc. syringe barrel (see figure 5).
6. Tightly rolled copper screening, 30 to 40 mesh per inch, approximately 3¼ inches wide and 30 inches long.
7. One hole rubber stopper.
8. DeKhotinsky cement.
9. Glass tubing. Inside diameter 8 to 9 mm. The long arm measures approximately 14 to 15 inches, the short arm 1½ inches, the distance between the arms 1¾ inches.

With the valve handle at number 3, approximately 30 cc. of water is admitted through the glass tube. Entrapped air is expelled by going through the same maneuvers as for gas analysis. More water is added and the entrapped air again expelled until the fluid just fills the

absorption chamber. The corresponding water level in the tube is marked 100. The valve is turned to 1, the plunger raised full length; the valve turned to 2, and the plunger slowly depressed full length. The height to which the water column rises in the tube is marked 0. The distance between the 0 mark and 100 mark is

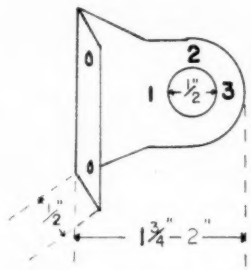


FIGURE 4. Numbered plate for valve. This is fastened to the side of the box (see figure 1) so that the handle of the syringe fits through the central hole. The position of the valve is indicated by the numbers.

divided into 10 equal parts and numbered in the proper order from 10 to 90. The space between each two markings is further divided to represent the 5 per cent levels. The water is removed by inverting the apparatus and turning the valve to position 3.

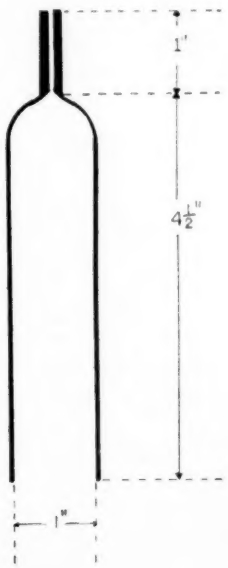


FIGURE 5. Absorption chamber for high concentrations of oxygen (over 85 per cent).

The absorption chamber may now be filled with the absorbing fluid and the entrapped air removed in a fashion similar to that described above. Set the movable scale with the 100 mark at the level of the fluid in the glass tube, and the apparatus is ready for use. The efficacy of the apparatus is tested by analyzing room air which should yield approximately 21 per cent oxygen.

THE ABSORBING FLUID AND CARE OF THE APPARATUS

The absorbing fluid must yield accurate and speedy analyses and should be capable of absorbing a large volume of oxygen before requiring renewal.

Approximately 100 cc. of the most satisfactory absorbing fluid for routine use in this instrument is prepared in the following manner: Dissolve 65 grams of ammonium nitrate in 45 cc. of water; add 15 cc. concentrated ammonium hydroxide. The apparatus when filled with this solution (approximately 30 cc.) will absorb about 400 cc. of oxygen before a sediment forms which may clog the pores of the

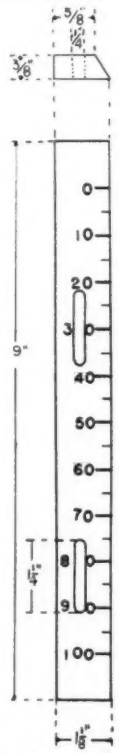


FIGURE 6. Adjustable scale to indicate calibration of glass tube. When mounted, the edge of the ruler overlaps the calibrated tube (see figure 1).

copper gauze and coat the calibrated tube. If facilities for glass blowing are available, a reservoir may be inserted in the long arm of the calibrated tube below the 100 mark. This will permit the apparatus to contain approximately 100 cc. of absorbing solution. The amount of oxygen which can be absorbed before it is necessary to clean the apparatus will be correspondingly increased. For concentrations of oxygen greater than 90 per cent[2] the solution described by Badger[3] is somewhat more satisfactory. This is prepared by mixing equal parts of water and concentrated ammonium hydroxide and saturating this mixture with ammonium chloride. This solution absorbs oxygen more rapidly than the ammonium nitrate mixture and the instrument will absorb about 650 cc. of oxygen before the

precipitate forms, but this strong ammonia solution fails to yield accurate analyses with low oxygen concentrations and tends to form a more troublesome precipitate on the copper gauze.

Soon after the precipitate becomes visible on the copper screening or in the calibrated tube it should be removed in the following manner:

1. Raise the top of the container. Connect the calibrated tube to an empty bottle by rubber tubing and the side arm of the valve to a bottle of unused absorbing solution (a 20 per cent solution of ammonia is less expensive but works more slowly).

2. Direct the unused absorbing solution (valve on 1, raise plunger, valve on 2 lower plunger, and repeat) into the absorption chamber until the old blue fluid has been replaced.

3. Remove entrapped air by turning the valve to 2 and raising the syringe plunger.

4. Allow the solution to remain in the absorption chamber until all visible sediment is dissolved (about 5 minutes).

5. Add fresh solution until the blue color disappears.

6. Disconnect the rubber tubing from the calibrated tube. With the valve on 2 raise the plunger and empty the calibrated tube to the 100 mark.

7. Clean and dry the syringe and lubricate the barrel with a small amount of liquid petrolatum.

8. Close and fasten the top. The instrument is again ready for use.

SUMMARY

An instrument for determining the concentration of oxygen within an oxygen tent is described. The directions for use are simple enough so that the apparatus can be used efficiently by a nurse or attendant without previous instruction or experience. The method yields results which are accurate within 2 per cent. Instructions and working diagrams are given so that the instrument can be built by anyone handy with tools. The retail cost of the necessary parts is approximately four dollars.

REFERENCES

1. Barach, A. L.: Oxygen treatment. J. A. M. A. **106**:725 (Feb. 29) 1936.
2. Fine, J., Banks, B. M., Sears, J. B. and Hermanson, L.: The treatment of gaseous distention of the intestine by the inhalation of ninety-five per cent oxygen. Ann. Surg. **103**:375, 1936.
3. Badger, W. L.: Determination of oxygen by the copper-ammonia-ammonium-chloride reagent. Indust. & Engin. Chem. **12**:161, 1920.
4. Van Slyke, D. D., and Sendroy, J., Jr.: Manometric analysis of gas mixtures. I. The determination, by simple absorption, of carbon dioxide, oxygen, and nitrogen in mixtures of these gases. J. Biol. Chem. **95**:509 (March) 1932.

THE PLURALITY OF STREPTOCOCCAL TOXINS*

BY SANFORD B. HOOKER, M.D.†

MY first intention to discuss only the differences among the erythrogenic or primarily rash-producing scarlatinal toxins has been modified. These toxins are not among the most destructive weapons of streptococci and the particular one that I have studied is of minor practical importance. So it seems more useful, on this occasion, to include some discussion of the whole known arsenal of this disabling and death-dealing tribe of micro-organisms. During the fifty years since streptococci were first clearly established as a genus we have learned much about their ubiquity, their hundreds of varieties, their changeable and diverse degrees of virulence, and the long list of diseases that they cause or complicate. We have come to appreciate very keenly the host of arduous and perplexing problems that confront the student of streptococci but our growing knowledge has barely now attained the stage of adolescence. There is still a long road to travel before we shall be able to control these micro-organisms but it may be confidently expected that we shall travel with accelerated speed because of improved technology, better training of investigators, and the development of more penetrating concepts. Among the latter there are none more profoundly significant than the one that recognizes the urgent need for a precise determination of those bacterial antigenic components or products that are of fundamental importance to virulence and to immunity.

Of the ten thousand papers dealing with the streptococcus many are devoted to such antigenic analyses. Scores of distinctly qualitative differences are demonstrable among some of the antigens present in any considerable collection of streptococci. A single strain may contain or elaborate several antigenic components whose activities are separable by appropriate methods. The already difficult analysis of such a mosaic structure is further complicated by the recently discovered phenomenon of bacterial dissociation whereby important antigenic constituents are often lost and less often regained or even changed. The structure thus becomes kaleidoscopic. There are so many impediments and well-hidden pitfalls that the most wary investigator is sure to be temporarily frustrated or entrapped, at least once, and more probably, many times.

Most of these analyses have been applied to those specific agglutinative characteristics that permit an allocation of some strains into "serologic" groups. As one who long indulged hopefully in this kind of botanizing among the green-producing (*alpha* or *viridans*) strepto-

*From the Evans Memorial, Massachusetts Memorial Hospitals, Boston.

†Hooker, Sanford B.—Professor of Immunology, Boston University School of Medicine. For record and address of author see "This Week's Issue," page 97.

cocci, the writer concluded that, in this group, no classification of service to medicine can be achieved by this method. There is such a bewildering variety of individualistic strains that among six hundred odd cross-tests there were less than three per cent of strong cross agglutinations, and no identical strains were found. The same extraordinary antigenic heterogeneity doubtlessly exists among the similarly saprophytic *alpha prime* and *gamma* types.

The (*beta*) hemolytic streptococci can be thus grouped to some extent; but, even in this more virulent species, antigenic diversity is pronounced. There is only a slight tendency toward an association of agglutinative groups with clinical entities.

There are reasons for thinking that our attention has been unwisely and too exclusively focussed upon minute differences in agglutinative specificity. The complexity of the maze into which we have thus been led, and the enormous obstacles to specific antibacterial therapy thereby interposed should, from an economic standpoint alone, encourage us to seek other, perhaps less tortuous, lines of approach to the ultimate therapeutic goal. With these considerations in mind we turn to a brief discussion of the types of streptococcal substances which may all, or in various combinations, be attributes of a single strain. They have been studied in greatest detail in connection with the more virulent hemolytic varieties. The term "toxin" is used in its broadest (clinical) sense.

HEMOTOXIN

This hemolytic substance, useful in the classification of streptococci, is very unstable. It is sensitive to moderate heat, is quickly oxidized to an inactive form, and is readily adsorbed by filters. In cultures, the production of hemotoxin begins early, reaches its height in eight to twelve hours, then rapidly declines. These characteristics obviously impede investigations of its chemical and immunologic nature.

Hemotoxin lakes a variety of bloods, including human. Intravenous injections of lytic filtrates into rabbits induce rapidly fatal toxemia or progressive anemia. These results do not follow the injection of filtrates previously heated only to 37 degrees C. for twelve hours; therefore they are more probably due to the highly labile hemotoxin than to other poisonous components of the filtrate from a young culture.

Hemotoxin is antigenic; it stimulates the production of an antilysin which neutralizes the toxins' hemolytic property. Following tonsillitis, scarlet fever, and other infections with hemolytic streptococci the patients' sera contain increased quantities of antistreptolysin. It appears that hemotoxin is antigenically species-specific rather than strain-specific. This fact will greatly simplify and cheapen the production of antihemotoxin should such an antibody prove to be medically useful.

The significance of streptococcal hemotoxin is difficult to appraise. There is some correlation between a strain's virulence and its ability to secrete a highly potent lysin although an avirulent strain may produce enough to cause a clear circumcolonial zone in a blood-agar plate. Many analogies make it likely that this toxin is able to damage tissue-cells other than erythrocytes. We must, then, not lose sight of the possibility that this difficultly investigable thermolabile toxin may be an important adjunct to pyogenicity and invasiveness—the most dangerous offensive properties of hemolytic streptococci.

LEUKOCIDIN

It is held by some that the hemolytic and leukocidal effects of streptococcal filtrates should be ascribed to a single substance. This position hardly seems tenable in view of the following differentiating characteristics: Leukocidin is produced during the early growth of streptococcal cultures but it persists much longer than hemotoxin, is distinctly more thermostable, more readily filtrable, and requires different optimal conditions for its production. Leukocytes specifically adsorb it and hemotoxin is left in a filtrate that originally exhibited a dual activity. Its effect upon leukocytes differs from that produced by the organic acids formed in cultures of streptococci.

Leukocidin is definitely correlated with virulence. It is antiphagocytic and in increasing concentrations kills and disintegrates leukocytes. Macrophages are more resistant than polynuclears. The potency of leukocidin may most neatly be measured by observing its effect upon the respiratory activity of leukocytes. The ingenious "bioscopic" method of Neisser and Wechsberg depends upon the ability of living leukocytes to metabolize oxygen and thus reduce methylene blue, in the absence of air, to a colorless compound. Leukocidin inhibits or abolishes this activity.

The antigenic properties of leukocidin have received practically no study. Ordinary antistreptococcal sera do not neutralize its activity but this may well be due to its inadequate representation in the material injected into the animals furnishing the sera. Thus is emphasized the imperative need, in producing effective immune sera, for inocula that contain a full complement of the antigens elaborated by living, fully virulent bacteria. The development of the agar-focus or blood clot method of immunization is a progressive step in this direction, but the production of adequately super-

immune serum may require supplemental injection of some antigens in more concentrated form and larger dose than can be supplied by small artificial foci of living organisms. There is one meager report that immune serum produced by injection of leukocidal filtrate does possess a neutralizing property, and that leukocidin is a species-specific and not a type-specific substance. From the economic and investigational standpoints the immense importance of such antigenic nonheterogeneity merits repeated emphasis.

Despite our very limited knowledge of this substance, it does not seem overbold to predict that leukocidin is destined to occupy a position of high eminence among the factors that contribute to streptococcal virulence. Any agent so offensively antagonistic to phagocytic cells—the indispensable bulwark of antibacterial immunity—deserves most thorough study. Our partial successes in controlling the streptococcoses are so restricted as no longer to permit a continuance of our neglectful attitude toward this pathogenic agent which so compellingly demands intensive investigation.

"EXOTOXINS"

The erythrogenic substances in filtrates of some hemolytic streptococci are responsible for the scarlatinal rash and the Dick reaction. They possess the one fundamental characteristic of true toxins, i.e., they are antigenic and evoke the production of an antitoxin which neutralizes according to the rule of multiple proportions. The existence of a streptococcal toxin had long been affirmed but our knowledge of its nature was broadened by the Dicks' use of the susceptible human skin as a reagent which permits some quantitative measurement both of toxin and its antitoxin.

The theory that the scarlatinal exanthem may be an allergic rather than a toxic manifestation has little to commend it.

There are wide quantitative differences in the potency of toxins derived from different strains; those of scarlatinal origin are usually the most powerful. This toxin is remarkably resistant to heat and the deteriorative effect of storage. These properties facilitate chemical investigation of its nature although accurate quantitation is hampered by the lack of a readily determinable and precise end-point.

There are distinct qualitative differences among some of the erythrotoxins produced by separate strains of hemolytic streptococci of erysipelatous, puerperal, and scarlatinal or other origin. These differences, however, may be just as distinct among separate strains from scarlet fever alone, and can even be clearly demonstrated in the filtrate of a "single-celled", pure-line, polytoxigenic strain. Our own study of this problem has indicated that the most important toxin, which we call "A" for convenience, is produced by the large majority of scarlatinal strains and elicits much the highest rate of positive cutaneous reactions. Toxin "B," first discovered two or three years after it had been patented, is unequivocally distinguishable by a number of immunologic and chemical criteria, is produced by a considerable proportion of strains but only a small number of people react to it. A given strain may produce either, both, or neither of these toxins. Trask and Blake have reported cases in which antitoxin was ineffective and from which were isolated strains whose toxin was not neutralized by an immune serum containing both anti-"A" and anti-"B." The difficulty of finding suitably reactive test subjects has hampered the characterization of these toxins, with the exception of "A".

These additional toxins are probably of minor practical significance in the control of scarlet fever but their recognition is important to an understanding of the mechanism of the disease, and in explanation of many apparent theoretical discrepancies which have been recorded. With "B"-toxin we have induced fever, rash, desquamation, eosinophilia, and conversion of the cutaneous reaction from positive to negative in an A+B+ reactor; the cutaneous response to "A" remained unchanged. Titrations of the "A"- and "B"-content of 414 filtrates from scarlatinal strains and comparison of toxigenic types with the cutaneous reactivity of patients tested early and during convalescence led us to conclude that the "B"-toxin is actively concerned in pathogenesis of scarlet fever in less than 10 per cent of the cases in this locality. Also with the co-operation of the Staff of the Haynes Memorial, we found, in 149 cases, no correlation between the incidence or kind of complication and the toxigenic potency of the patient's "B"-producing strain. The only arthritic complication developed in a patient whose strain was a very feeble "A"- but potent "B"-producer. Coburn has reported an institutional epidemic of rheumatic fever apparently caused by a similar strain, but it cannot yet be said that "B"-toxin has a predilection for any special tissue.

The minor practical importance of "B"-toxin is further lessened by the fact that antitoxin for "B" is plentiful in most immune sera. This multivalency is sometimes fortuitously due to immunization with several strains, one or more of which would be likely to possess the rather common property of producing "B", or to the purposeful selection of a single strain, such as "N. Y. 5," which produces at least both "A" and "B". It is obvious that for active immunization of either man or animals a toxic

filtrate of broad antigenic scope should be chosen.

In attempting to weigh the importance of streptococcal exotoxin one should remember that our knowledge of it is of but a few years' growth. Its discovery has broadened our comprehension of the pathogenic mechanism, but has by no means solved the problem of controlling streptococcal infection. Exotoxin is not an especially malignant weapon of the streptococcus and rarely exerts a dominant influence in fatal infections. That an antitoxic immunity, however, is of some importance in aiding recovery from infection is indicated by at least three lines of evidence: (a) The large majority of those who have used antitoxin early in the treatment of scarlet fever agree that the incidence of septic complications is lessened; (b) individuals actively immunized with toxin often contract scarlatinal tonsillitis but further septic complications appear to develop less frequently than among those who lack antitoxin and contract typical scarlet fever with exanthem; (c) rabbits injected with sublethal doses of cocci die if a sublethal amount of toxin is also injected, and rabbits injected with virulent toxigenic streptococci live much longer if they are treated with a purely antitoxic serum —one devoid of demonstrable antibacterial factors. Thus a defensive mechanism relieved of the burden of combating intoxication is the better able to cope with the more strictly infectious—pyogenic and invasive—forces.

"ENDOTOXIN"

The endotoxins are assumed to exist preformed in the bacterial cell and be liberated upon its disintegration. Some have thought that this kind of toxicity is due to poisonous protein cleavage products resulting from the action of the host's cellular and circulating enzymes upon the bacterial cell. The term endotoxin only cloaks our ignorance. In a recent book on streptococci the use of this unprecise and uninformative word in a special sense connoting virulence and specific tropinogenesis, does not promote clarity of understanding. It is much more probable that leukocidin, fibrinolysin, and the haptens to be mentioned are the factors most important to virulence and antibacterial immunity. Progress will be delayed if we cannot characterize these factors with more particularity than the term "endotoxin" can ever permit.

POLYSACCHARIDES

Since the pioneer work of Zinsser on "residue-antigens" it has been revealed that these "soluble specific substances" are complex carbohydrates which belong to the class of haptens—separable components of many antigenic materials, including bacteria, which condition specific reactivity but lack a truly antigenic power or possess it in a restricted sense. The streptococcal polysaccharides resemble those of the pneumococci in such features as stability and association with the capsular or ectoplasmic substance of the bacterial cell. They permit a serological separation of hemolytic streptococci into groups rather than types, and the group "A" of Lancefield comprises the vast majority of those strains that are of the greatest pathologic importance in man. The further significance of streptococcal polysaccharides is doubtful. They have been shown to be abundantly present in nonvirulent (although potently toxigenic) strains but these were *not* effective antibacterial immunizing agents.

TYPE-SPECIFIC PROTEIN

This substance, extractable by dilute hydrochloric acid, seems to be a component that allows the separation of streptococci into antigenic subgroups or determines the behavior of individualistic strains in agglutination, precipitation and in other serologic reactions. Although of proteinic nature, curiously enough it behaves as a hapten, i.e., it has not yet proved capable, in the pure state, of stimulating the formation of antibodies. There is a suggestion that it is of more importance to antibacterial immunity than to virulence, as indicated by the observation that a strain of *attenuated* virulence may contain its full complement of this protein, and, be a good immunizing agent; an avirulent strain deficient in this protein did not evoke protective antibody. Inasmuch as a given specific protein is shared by relatively few strains, the disadvantage to practical serum therapy is at once apparent.

Some unpublished observations by Stuart Mudd, an able recent recruit to the active students of streptococci, relate to the discovery of still another specific, highly unstable hapten probably of proteinic nature, which is importantly involved in phagocytosis. Further disclosures of the relation of this substance to virulence and immunity will be awaited with interest.

It may not be out of place here to mention the speculative idea that "toxins" in the nascent state may have a special significance.

"NUCLEOPROTEIN"

This material, probably a conglomerate, is antigenic but possesses little differential specificity. An immune serum prepared with nucleoprotein from a hemolytic streptococcus reacts with nucleoproteins from S. viridans, pneumococci, staphylococci, and probably other microorganisms. It is not yet demonstrably significant in immunity.

FIBRINOLYSIN

About three years ago Tillett and Garner reported that some human strains of hemolytic streptococci produce an agent capable of dissolving clotted human (but not rabbit's) plasma; sera from patients recently recovered from streptococcal infections were able to neutralize this lytic effect upon fibrin. There have since appeared a number of brief papers dealing with fibrinolysin; fortunately, it is rather more species- or group-specific than type-specific; its importance as a factor which, by preventing the accumulation of fibrin, effectively antagonizes the protective localizing effect of inflammation can be strongly suspected. Antifibrinolysin should prove to be a notable antiinvasive agent of resistance, perhaps most critically important in the very first stage of infection.

MISCELLANEOUS AGENTS

"Aggressin", "virulin", "subhemagglutinin", "endotheliotoxin", and "myotoxin"—products of the christening urge—are probably but other names for the several substances we have discussed.

Streptococci also produce a variety of enzymes which are indirectly associated with virulence only because they are more or less essential to bacterial metabolism and life; their connection with immunity is unknown.

The foregoing discussion is not intended to be a rehearsal of the past achievements of immunologic enterprise; it is more an attempt to point out the wide gaps in our knowledge, to draw attention to some neglected phases of the problem, to suggest that others have possibly been overemphasized, to indicate the investigational economics of certain species-specific antigens, and, above all, to urge the necessity for further correlation of antigenic analyses with the factors of immunity to natural infections.

THERAPEUTICS OF DRUG HABITS

BY ALEXANDER LAMBERT, M.D.*

IT was with genuine pleasure that I accepted the kind invitation to appear before your Harvey Society and discuss for you my experience in the therapeutic care of certain drug addictions. I realize that I am deviating from the usual run of scientific research not to offer you some added facts for your use in the diagnosis of disease or draw your attention to certain new viewpoints in the course of the morbid processes, but it seems wise to me for physicians to discuss, occasionally, the therapeutic care of the sick.

In the last thirty or forty years, as the accuracy in diagnosis of disease has increased and our knowledge of the morbid processes, which we group together as diseases, has been more accurately appreciated, the scepticism in the profession of the value of medicinal treatment has also increased greatly. This has been an advantage in some ways, but it has had the disadvantage of driving many patients to the care of various cults or to self-medication, based on the attraction of the advertising of the drug manufacturers.

Drug habit is best defined as the habitual use of any drug for the purpose of avoiding the emotional strains of life which are too intense for the personality to support. To confine drug addiction to the persistent habit of the use of the opium derivatives is altogether too narrow a conception to be of any real medical value. The least severe strains of life are those which cause sleeplessness, and the drugs taken for relief are the hypnotics. The more severe strains are those in which narcotics are used, either alcohol or opiates. The relief demanded and obtained is often a psychologic necessity.

It is a noticeable fact that, when seeking or obtaining pleasure and recreation, the loss of sleep is thought but little of, and the ability to lose sleep and the next day go on with one's existence is often a matter of pride. But, when the worries of life are so severe that they inhibit sleep and one must toss and worry and vainly strive to forget the day's strains and troubles, the loss of sleep is looked upon as a severe misfortune and a strain that cannot be borne without immediate help. The average person can face life fairly well if he can obtain sleep and be ready to face his work when daylight comes.

One of the oldest hypnotics, and really one of the best, is chloral hydrate. In the sleep obtained with it the patient can wake naturally and drop off to sleep again. The drug is especially good in the early years of life. It has a habit connected with its use and, two or three generations ago, its use was a common habit through which weary people could obtain relief without using either alcohol or the opiates to excess. It suffices in most instances, but it has the peculiarity, if given to old people, of causing a type of sleep-walking in which the patient becomes active in the middle of the night, be-

*Lambert, Alexander—Formerly, Professor of Clinical Medicine, Cornell University Medical School. For record and address of author see "This Week's Issue," page 97.

ing unable to separate the sleeping from the waking consciousness. The patient wanders up and down the room or goes running through the hall, noisy and perturbed, and is utterly unconscious of so doing. These patients worry the household, but frequently the next morning consider that they have had an excellent night, as they have no memory of what they have done.

The habit obtained through the persistent use of chloral was formerly considered a very difficult one to break, chiefly because, at that time, the profession did not understand the psychologic basis on which the habit was formed. But, in reality, it is no more difficult to cure this habit than any other one of a similar type from the hypnotic drugs. Chloral is often used in combination with the bromides. The latter, persisted in, produce a deterioration in the normal judgment of the patient. The bromides may produce delusions, so that the patients become inaccurate in their statements and ideas and may even go into a definite drug psychosis. Bromides are much more apt to produce this effect than they have been credited with in these conditions, and the recovery from bromide poisoning is slow.

The most common hypnotics of today belong to the barbituric acid group, which began a little over twenty years ago with veronal. It has run through a large number of variations, in which each chemist has endeavored to substitute some variation in chemical constitution that would leave the hypnotic powers intact, or increase them, and would avoid the very evident evils of the perversion of personality which these drugs can produce. The injury of the barbiturates, when they do poison a patient, produces a much greater injury to the personality than do morphine or the other opiates, and the deterioration is much more severe and lasting. All patients are not necessarily poisoned by ordinary hypnotic dosages of these barbiturates. Some forms of barbiturates are much more likely to poison certain people than others, but I have yet to find a barbiturate, and I have tried and experimented with most of them, which will not distinctly poison and pervert the personality in some patients. Various barbiturates can be gauged in the intensity of their sleep-producing qualities and in the rapidity in which they are eliminated from the body, reducing the danger of poisoning from their use. But, in several of them, even in therapeutic doses, the borderline between safety and danger is too slight to be safe.

Veronal, the original drug of this type, has in many instances proved to be an evil drug, and hallucinations, delusions of persecution and an ugly resentful distortion of personality are usual after its habitual use. In the mildest intoxications it leaves patients ill-natured, sharp-tongued, suspicious and mean-tempered, preferring to say the mean thing rather than the pleasant one and giving the patient a reputation for meanness of disposition which is done in such a natural way that the drug goes unsuspected. The patient carries the full blame, when the trouble is, in reality, a real drug poisoning and the patient is unconscious of the perversion which the drug has produced. Veronal and other forms of the barbiturates are not infrequently used with suicidal intent, and large doses produce coma lasting many days, from which it is difficult to rouse the patient.

When a psychosis has once been established through the use of the barbiturates, it takes weeks, if not months, to bring about recovery under the best conditions of institutional care. The treatment for this form of drug poisoning in the acute cases where the perversion is noticeable, but of mild extent, is to change the form of barbiturate or, better, to change the hypnotic, seeking for one that will not produce the same heaviness of head in the morning or the same intense disagreeable reactions to the ordinary situations of life. The physician should be alive to the fact that changes of disposition in his patients may be due to the drug which he gives and not to the patient.

In severe genuine poisoning by the drug, the patient may become utterly irresponsible in his actions, inco-ordinate in his muscular movements and entirely unable to go on with his ordinary existence. The amount that these patients can take seems phenomenal when one considers the ordinary dosage that is necessary for hypnotic use. I had a young patient, a medical student, who had acquired the habit of easing the pain of infected sinuses with codein. He was taking daily 28 grains of this opiate and had added to this the barbiturate acid preparation, nembutal, which, as you know, is usually taken in capsules of 1½ grains each. In order to obtain sleep, he was regularly taking 24 capsules a day, that is, 36 grains a day. He was reduced to an ordinary stupid dilettante in all he attempted to do. The rapidity with which this special type of barbiturate is eliminated had saved him from a severe poisoning, and it was necessary only to cut off his barbiturate and to rely on the codein until he had reached his normal equilibrium of activity, then proceeding, as we shall see later, to cut him off the opiate.

Many patients are not so easily relieved of their drug. Sodium amytal seems to be a very favorite form of drug habit, because it is a vigorous hypnotic. It has the peculiarity in many people that, when they awake for a few minutes, they do not clearly separate their waking from their sleeping consciousness and are very apt to be pugnacious and to harm people. We tried this drug in the Bellevue Hospital to relieve the distress and pains of the with-

drawal symptoms of morphine. Several vigorous underworld addicts woke up from their sleep and, before they could be quieted down, had destroyed most of the furniture in their environment and required the full attention of all the orderlies. Its intravenous use is a favorite method with some of those addicted to it. These individuals will have a disassociation of consciousness with complete forgetfulness, but, as one converses with them, they seem to be only slightly intoxicated. They are inaccurate, of course, as in other intoxications, in their speech and in their ideas, but not enough to make one realize the absolute disassociation that has taken place. The next day, when they recover from their sleep, they will have absolutely no recollection of what they have done or said.

Some patients can take enormous doses of sodium amytal ingested orally. One patient I have had was taking, when she was brought to me, 30 capsules a day of the 3 grain capsules. She could not go on without it and, if suddenly deprived of it, suffered from severe convulsions. This patient was incoherent in speech and incoordinate in her muscular actions; her face was so changed from its normal expression that she looked like a wild, idiotic type of person, although normally of a fine character. This patient was deprived of her drug, has remained free from it and is living a happy, normal life.

An excellent treatment for these severe barbiturate poisonings is the use of picrotoxin, the bitter principle from the seed of *Cocculus indicus*. It is obtainable in ampules containing 3 mg. in 1 cc. Its physiologic action is a respiratory and vasomotor stimulation through the medullary centers. It can be administered intravenously, subcutaneously or orally. If the barbiturate poisoning be from a large dose of a quickly absorbed barbiturate as pentobarbital, pernocton, amytal or alurate (the barbiturate of allonal), a large single dose, as 1 or 2 cc., of the above solution intravenously is recommended in a person of 150 lbs. If there are no toxic symptoms of twitching of the arms, increased respiratory rate or rise in blood pressure from this, the dose should be repeated in twenty minutes. As the patient improves, the medication can be given orally in the dose of 3 mg. at varying intervals until the patient is lucid. In the poisoning by the slower acting barbiturates, such as phenobarbital, noctal or barbital, the medication can be given orally or subcutaneously in a dose of 6 mg., followed by a 3 mg. dose after an hour and continued at such intervals until the barbiturate poisoning is evidently passing off. In chronic poisoning, 3 mg. every six hours is helpful in detoxicating the patient.

In the patients who remain unconscious or have been in coma for one or more days, it is wise to give immediately intravenous injections of glucose, giving 25 cc. of a 25 or 50 per cent solution. Such medication seems more effective if subcutaneous injections of insulin are also given. It is wise to take for granted that these patients have some insulin of their own and, instead of giving the exact amount of one unit of the insulin for every 2 gm. of sugar, to give two thirds of the amount. These intravenous injections of sugar can be given once or twice a day. They keep up the nourishment of the patient and are well borne. As these patients are recovering from their chronic or acute poisoning, they are nervous and apprehensive and their nervous systems seem generally unstable. This instability, chiefly of the autonomic nervous system, is very much calmed and improved by the use of a new drug, diphenylmethylpyrazonyl, sold under the name of "rossium". It is a double molecule of antipyrin and the dosage here is a gram every four hours.

A new type of hypnotic, which is proving of value, does not depend on barbituric acid for its action. In this group are the various combinations of carbamide, which have been produced; one, bromural, is a mild hypnotic and another is sedormid, which possesses a certain quality that the barbiturates do not seem to have. In some people the barbiturates are effective to produce sleep, but do not have, in small doses, a sedative action which quiets the patient and often gives sufficient soothing effect for sleep to come naturally. In moderate doses these carbamides are effective for the sedentary effect is pronounced and, unless too much is taken, the heaviness of the morning after is not marked. If too large a dose is taken of these carbamide hypnotics, there is a very decided heavy headiness, a dullness of mind and even a blurring of speech. They do not seem to pervert the personality except in very large doses. One patient of mine collected eighteen tablets of sedormid and took them at one dose, because he wished to get, as he said, the full effect. This dose produced delusions and an active delirium. At the end of four days, when he regained his mental equilibrium, his curiosity was thoroughly satiated.

The general treatment of all these problems which bring about various intensities of hypnotic drug-taking lies in the emotional training of the patient. In general it is the unsolved problems of life which produce the restlessness and cause both the sleeplessness and many other problems of existence. All worries and problems of life cannot be solved by the physician, but he can help the individuals to overcome their own problems and to realize that the solution is obtained only by facing and not by dodging them. Of course, all marital misfits cannot be solved even by facing the facts and all the petty,

mean self-centered selfishness cannot be entirely rearranged, but facing the situation will solve it quicker than the incessant use of hypnotics. If this is done and the cause is realized, many patients that now go untreated and become poisoned will be relieved of their worries and their drug addictions simultaneously.

The problems of life, which seem at times to defy solution, are those for which alcohol and the opiates are taken. The fundamental basis of alcoholic drunkenness and morphine addiction is essentially the same. The periodic alcoholic, who, at varying intervals of time, drinks to dumb forgetfulness, does it on the same psychologic basis as the morphinist who takes his drug habitually to avoid the unhappiness or responsibility that he is unable to face. The blame does not rest on a weak will, as is so often claimed, but it is a question of emotions. When the emotions are too disagreeable and too intense to be harbored, either temporary or continuous relief is sought in alcohol, or permanent relief is obtained through morphine. The habitual indulgence in these two drugs has been universally looked upon as a moral degradation. Curiously enough, in those countries in which alcohol is more or less condoned, the opiates are condemned. In the Western nations and Japan, alcoholic indulgence is condoned, but morphine addiction condemned; in China, India and the East, opium is condoned, but alcoholic indulgence is condemned. It is, therefore, a question of custom and convention, not of morals, which controls, and each country, by condoning the narcotic relief which unhappy humanity demands, condemns vigorously all those who do not conform in their choice of narcotics to the customs and conventions of that country. It is, perhaps, best summed up by saying that, in the tragic conflict between what man has been taught he should have and what in life he has been allowed to obtain, man has found in alcohol and other drugs sinister, but effective, peacemakers.

Alcohol, when taken to excess, produces changes in the parenchymatous cells of certain viscera; and, following this destruction, there is a connective tissue replacement. It therefore leaves a permanent injury behind its excessive use. Morphine, on the other hand, though indulged in for years, leaves behind it no recognizable pathologic change; it seems to be a functional cellular poison. When the morphine is taken away, the nerve tissues which were poisoned return to normal function. Clinically an alcoholic patient, who has suffered the morbid processes of a Korsakoff syndrome, is left with a personality, the finer emotions and values of which are hopelessly burned out. That personality never regains its former charm and previous sense of emotional values. There is no such change in the personality remaining after a morphinist has ceased to use his drug and his physical health has been regained.

Alcohol's earliest toxic effect is shown in its atrophy of judgment, and its hypertrophy of self-conceit. Of course, the exact degree of sensitiveness varies with each individual, and it rests upon the ability of the liver, or some other tissues, to hold back the alcohol from going into the circulation. But, when once the circulating blood holds a certain definite percentage, alcohol will go to the brain and the brain will soon absorb the same percentage. One part in a 100 does not produce drunkenness, a little over two parts in 100 produces the beginning of an expansive feeling and, by the time that three parts in a 100 are present, all human beings are drunk. The "strong head" of common parlance lies somewhere else in the body than in the brain and signifies that that individual possesses a power not yet understood which keeps the alcohol away from the brain. In judging excess it may be said that, if an individual is saying things he would have otherwise left unsaid or doing things he would, without alcohol, have left undone, alcoholic moderation has been exceeded. Such a physiologic excess of alcohol, if continued, is sure to bring harm or injury to the mental and physical make-up of that individual.

Considering the use of alcohol as a narcotic, there are distinctly two types of alcoholic excesses. In youth, alcohol is more often used to cut off emotional inhibition and the feeling of restraint which prevents the freedom of speech and action which customs and convention inhibit. In order to enjoy life more abundantly and to know through its own experience, youth vigorously resists authoritative restraint and uses alcohol to obliterate, or at least to inhibit, such restraints and to be free to experience for itself the full emotional rush of life without intellectual inhibition. In youth imagination and emotion enormously predominate over intellectual balance and over the controlling influence of judgment, for judgment, the most valuable of mental attributes, develops the most slowly. Drunkenness, when it occurs, is, therefore, not what is desired, but a side-product of the use of the drug. In the majority of instances, experience soon teaches that this form of alcoholism is neither the answer to life nor the solution of its problems. With this lack of value, it is usually discarded.

To those who have never had to adjust their emotional balance to their environment and their life, or to those who have unsuccessfully tried, the use of alcohol is the easy method of balancing a mental deficit. It cuts off the sense of inferiority and blunts the sense of failure. When under its influence, it, above all drugs, gives the sense described by Jack

London as that of "White Magic"—whatever is done or said, no matter how insignificant, seems to be the most perfectly done and the most brilliantly said. Individuals sensitive to alcohol drift unconsciously into its habitual excesses. Frequently a single drink is sufficient so to distort their judgment that they go on into an excess which may end in several days' debauch. The social customs of our race are such, and have been from time immemorial, that alcohol goes with good fellowship and hospitality, and not a few persons, sensitive to alcohol, drift into an excess that is unconscious and not of vicious origin. By the time a man reaches the early thirties, he knows whether his opportunities offer him a success which he can obtain through vigorous struggle. This means hard work and self-restraint and cannot be won with an alcoholic handicap added to it. It is at this age that the greatest number of young men, if they have been drinking to excess, give up their alcohol. If they do go on, they pass into the psychopathic group, in which, like older men, they drink to forget. The older group of alcoholics, who have been through life and felt its failures, have been through unhappiness and felt its bitterness or, through some uncontrolled factors, have failed of success find in alcohol its full narcotic value, and they learn to use it for its pure narcotism. These men do not get drunk because they drink; they drink that they may get drunk and obliterate all consciousness. Alcohol from time immemorial has been the last remaining solace to those who go down in defeat.

In treating alcoholic patients it is useless to argue with a mind that is poisoned with alcohol. It is a waste of time to appeal to or try to rearrange the befuddled intellect, hoping to obtain any balance of emotional control. The first thing to do is to put him to sleep and to see that he sleeps quietly long enough to unpoison his nervous tissues and to free his body from his narcotic. As soon as possible a vigorous mercurial purge should be given which aids enormously toward this result. Ordinary hypnotics in ordinary doses are insufficient to deal with patients poisoned with alcohol. Paraldehyde is one of the best drugs, disagreeable as it is with its unpleasant odor on the days following. Two drams repeated in half an hour, if the patient is not asleep, is a moderate dose for the average patient. This is better given with orange juice and a little whiskey, which takes the repulsive taste away from it, or it can be given simply with orange juice. It can also be given in plain cold ice water. This drug has the advantage of acting quickly. A combination of 25 to 30 grains of chloral, 1 to 2 grains of codein and 30 minims of the tincture of hyoscyamus at a dose is another excellent hypnotic. This should also contain with each dose, a few drops of tincture of capsicum and tincture of ginger, or some such stomachic which will stimulate the stomach to absorb. An alcoholic gastritis is notorious for its inability to absorb medication and the gastric mucous membranes should be stimulated to absorb with each dose.

Most of the barbiturate acid group of hypnotics, if given in the amount necessary to put an alcoholic asleep, will, in my experience, cause an increase of resistance and antagonism which the alcoholics so easily show. They become uneo-operative; and, an alcoholic, feeling sick, unhappy and in an ugly resistant mood, is a disagreeable patient to have anything to do with. It is useless, in my mind, to add to the difficulties of the situation in dealing with them. The alcoholics are always too eager to grasp at any excuse by which they can dodge the responsibility of freeing themselves from their narcotic and the barbiturate acid group of hypnotics is very prone to add to the normal obstinacy and resistance of these patients. The alleged thirst for alcohol, as far as its physical exhibition, occurs only in the first twelve or twenty-four hours after a debauch when they are recovering. The patient usually has obtained the temporary relief he has sought and is disgusted with himself. As his intelligence begins to control him, he is anxious to be rid of his alcohol and to be helped to cut it off as quickly as possible; but, many of them cling to the narcotic as long as they are permitted.

Recently I have used a new drug, diphenylmethylpyrazonyl (rossium), to quiet the excessive nervousness of alcoholics and even shorten the period of mental aberration in the delirium tremens. This given in gram doses every four hours does seem materially to shorten these excessive nervous symptoms. I shall discuss the drug more fully in dealing with the morphine habit.

It is useless to annoy the alcoholic you are tapering off with many little drinks of whiskey. If you decide to taper down rather than cut him off abruptly, it is wise to give him a comfortable drink of 2 ounces at a time at stated intervals. He will sober up much more quickly than if you annoy him by handing him half an ounce at a time. The younger the patient, the more abrupt should be the tapering.

Nearly all excessive periodic drinkers, especially women, drink from the pathologic point of view. There is something in their consciousness, the bitterness of which they will not, or cannot, face. In youth, it is usually the disappointed affections or the tragedies of personal friendship; as men grow older, it is more often the failures in the economic side of life and their inability to succeed or disappointed ambitions which crowd in the foreground. All through life, it is the maladjustments to hid-

den injuries and hidden distortions which must be sought for and worked out; but, it is invariably a psychologic rearrangement that has to be made. Most of humanity are concrete thinkers, unable to abstract their ideas. It is difficult for them to appreciate that it is the emotional impulses of life which are the mainsprings of action and that they can be just as wilful and strong-minded to get and take a drink, as they can be to resist or to do anything else. This they do not wish to realize, but incessantly look for some excuse or some reason to dodge this responsibility of emotional control. They therefore turn toward concrete ideas and believe that there must be some method of treatment or some substance which, if handed to them, will prevent their drinking. In this, their friends and relatives agree with them, and beg you to give them some secret thing, which will prevent their going out and physically raising a glass of whiskey to their lips. After you have sobered a man up and explained the situation to him and he leaves you to keep again his sobriety, he still will desire and look for a concrete medicine that will act as a chaperon to stop him from doing a physical act.

Alcoholics are among the most suggestible of human beings and for that reason, a routine line of treatment appealing to this universal suggestibility will enable them to regain self-confidence and encourage them to try for their own reconstruction. This is the basis of a large number of definite, so-called "cures". Suggestibility is useful as an adjunct to the psychologic rearrangement of the patient, but it is insufficient to obtain its object unless properly applied and made to co-operate with the psychologic rearrangement of the patient. It is impossible to go into all the innumerable psychologic details of each type of personality and their varying conflicts; but, remember this, that you will need, in dealing with them, an unending patience, a sense of humor and a cheerful charity toward the frailties of mankind. Also, never forget this fact concerning them, that these patients will never try to do any better than they think you expect them to do. They are always looking for an excuse not to try and it is in these patients that the human mind best shows its unlimited power of self-deception.

Considering now the morphine addict, in this country morphine addiction is condemned just as bitterly whether it be accidentally acquired through the legitimate practice of medicine against sickness or physical suffering or whether it be through an ennui of life and the inability to face it. All patients are alike condemned by public opinion; there is no charity for a patient who unwittingly finds himself caught in the toils of morphine addiction.

Among the morphinists, more than with the alcoholics, you find those who began life with inadequate personalities—those whose environment has forced on them a bitter realization of poverty and lack of opportunity and in whom the struggle for existence seems hopeless from the very beginning. Morphine forms, in that type of inadequate personality, a balance which enables them to muddle along in an existence whose bitter edge is blunted. In any group of opiate addicts found in the hospitals today a high percentage of inadequacy of personality will be a striking factor. The really average normal personality in such a group will average about 13 per cent; the rest of them vary in their degrees of inadequacy. A noticeably large number will show a tendency toward dementia praecox which brings with it the factor that they never can get in touch with existence to solve their problems. They are sensitive and easily hurt. They are cold-blooded and selfish in their actions toward others and unable to face reality, they quickly seek a drug by which they can avoid it all. There is a certain other group of inadequate personality which is very noticeable. These patients are not insane and, although they may be sufficiently intelligent to succeed in life, their intelligence, however keen, seems unable to control their emotional life. When their minds are filled with antisocial resentment, they easily fall victims to the chronic indulgence of opiates or alcohol. The problems of this group must be solved by Government control and will be referred to later. Members of the manic-depressive group are more in touch with their existence and are not so liable to form the morphine habit. The recurrent type of manic psychoses forms a large number of periodic alcoholic patients and also a smaller number of those addicted to morphine. They take these drugs to keep up their excitation as the manic excitement begins to subside; they end either with a spree in alcohol or, if addicted, to morphine or heroin. They resent being deprived of their drug and soon relapse.

There is a great difference between the patients who have taken opiates for physical pain and those who have taken them for psychogenic reasons. The prognosis is vastly different. Those, who have found themselves cursed with the morphine habit unknowingly through pain, will, at the earliest opportunity, endeavor to be rid of it. They dread its continuance, they resent the fact that they have it and are eager to be relieved. In most instances, it has been the excessive pain, misery and discomfort of the withdrawal period that has kept them from getting free from their habit. It is pretty nearly impossible for people to get themselves off without help. It can be done and I have seen several do it, but it is very unusual. It requires great tenacity of purpose, great ability to suffer pain, and great courage; but, when once off, this group of patients will almost invariably

stay off, unless their pain returns or they are given morphine unwittingly.

For years there have been many facts observed in the acquisition of the morphine habit, and many peculiarities concerning it that have defied explanation. The opiates are not like other drugs. They cannot be taken like an ordinary dose of atropine or of hyoscin for long periods and be dropped with no reaction. Every normal individual who ingests morphine in small doses for a certain length of time invariably acquires the so-called habit—that is, he will go through such a period of discomfort and misery that it is exceedingly difficult for him to cease taking the morphine. These symptoms of withdrawal last for about seventy-two to ninety-six hours and, then, cease of themselves. Why is it that a patient can take morphine or any opiate in daily injections for a week or two weeks, even up to eighteen or nineteen days, and can cease to take it without withdrawal symptoms, whereas, if the morphine is continued up to twenty-three or twenty-five days, that patient will find himself facing the distressing withdrawal symptoms? Codein will form the habit in the same way, but requires a much longer time than morphine. In ordinary doses, a patient can take codein for a month or six weeks before acquiring the habit, but if it is used to replace morphine, the patient acquires the habit more quickly. Heroin, diacetylmorphine, apparently will produce a habit in about a week or ten days if taken in ordinary doses. Dilaudid takes a little longer than morphine. Any opiate which possesses the power of obliterating pain and producing a sense of euphoria will, with rare exceptions, give the withdrawal symptoms similar to those of the morphine habit. Dionine, ethylmorphine, gives no sense of euphoria and yet will produce the habit much quicker than codeine. Paramorphine, dihydromorphine, produces a marked euphoria. It is weaker than morphine in its analgesic properties and yet requires a longer time than codein to produce the habit. The other new preparations of codein and of morphine should all be used with the same precaution as morphine against the habit.

The human organism tolerates astonishingly large doses of morphine in an addict without noticeable symptoms of acute intoxication. Some patients take daily from fifteen to twenty times the lethal dose for a normal person. I have seen a patient take 60 grains of morphine three times a day without discomfort and without apparent injury. Why do not these patients die from the intoxication of morphine? The word "habit" does not explain it. The morphine addict has a certain definite dose to which he becomes accustomed, but as time goes on there is a slow and increasing demand within him for an increase of the dose. If he does take a larger dose than normal to tide him over some period in which he cannot get his morphine, the added dose does not give a proportionately added period of time in which he is comfortable. Ostromislensky reports that in some addicts there is a very definite minimum dose of morphine needed to prevent them from suffering the symptoms of definite morphine hunger and that this dose can be measured with precision to within 13 milligrams. After a patient has been through the withdrawal of morphine and apparently relieved of his need for the drug, he actually differs from the normal individual, since, even after several years, a subcutaneous injection or ingestion by mouth of an insignificant dose of morphine, given unknown to the patient, may produce a relapse of his addiction.

The minimum dose of morphine needed by an addict may be replaced by quite a definite quantity of some derivative of morphine or other opiate. One unit of morphine is equivalent to the addict to 8 units of codein, to one third of a unit of heroin or to one quarter of a unit of dilaudid. Furthermore, the ease with which one can withdraw the opiate is vastly more in proportion to the length of time the addict has been taking his drug than it is to the amount that he has been taking. It is no more difficult so far as the suffering of the patient is concerned, to withdraw 30 grains a day from a patient, than it is to withdraw 10 grains or even 5 grains; but, it makes a vast difference whether he has been taking it for less than a year or whether he has been taking it for ten or twenty years or longer. Why is it that, in dealing with this poison, the distressing and ominous symptoms, which may even cause a fatal outcome, appear in the addict after the withdrawal of the poisons? At the height of an addiction, morphine produces no pleasant excitement and no blissful repose, and, yet, in the normal individual the narcotic effects occur almost without exception.

Another interesting fact is that a baby of a woman addicted to morphine not infrequently will show at birth the need of morphine and will die unless it is given to it. The baby will live and thrive on a small dose of opiate and this should be kept up regularly until the child is old enough to stand withdrawal. At such a time the opiate can be easily withdrawn and the child will have a healthy life. I have personally taken care of two such children, one little girl of nine years and one of fourteen. They both went through the withdrawal of their addiction very easily and went on to a normal existence. Each of these children had been taking laudanum from birth.

Of the various older theories about morphine addiction, that of Bishop best explained the clinical facts. He believed that morphine injected into the body produced a special substance which he designated as an antitoxin and

that this antibody reacted with the morphine, and prevented the injury to the organism by the morphine. In excess, this antitoxin produced withdrawal symptoms, hence the necessity of continuous doses of morphine in the addict. This theory helped to explain a good many of the above facts, but it failed to explain the fact that, when a patient is once relieved of this addiction, years afterward the ingestion of even a small dose of morphine may again cause the habit to be rapidly formed. Moreover, all attempts to isolate this antitoxin have failed and Pellini has shown that the blood of morphinized dogs contains no poison at the time of withdrawal.

Among other theories, that of Ostromislensky is today the best working hypothesis. This physician believes that morphine addiction is an example of allergy. The antigen necessary to produce this condition is not the morphine itself, but a combination of morphine with some body proteid. This neutralizes the morphine and the combined antigen, in the early stages of the morphine taking, circulates harmlessly. Until sufficient antibody is formed to act with this combined antigen, addiction is not produced and withdrawal of the morphine will not cause symptoms. The antigen or the antibody in small doses or the combination of antigen and antibody in the early days of their formation do not seem to cause sufficient reaction to poison the individual. The antibody is a permanent formation in the nerve tissues or elsewhere, which can remain there for years. If morphine is ingested, combined antigen is produced which, meeting again with the stored up antibody, again produces the habit, even when the morphine is taken without knowledge of the patient. The withdrawal symptoms of morphine are an exhibition of anaphylactic shock. The excess of antibody does not cause the shock. The combined antigen is lacking the morphine constituent and it is the combination of the antibody with this unsatisfied antigen that produces the shock. That such a combination of drugs can occur has been shown by the work of Landsteiner, as quoted by Bray in his interesting book on allergy. Antigens have been shown to pass through the placental circulation from mother to fetus. Ostromislensky, moreover, reports his failure to cause solutions of morphine to pass from the maternal to the fetal circulation of the human placenta.

Ostromislensky, following out this theory as his working hypothesis, noted that Matsuda found that antipyrin, phenyldimethylpyrazolone, prevented the death of guinea pigs in anaphylactic shock. He, therefore, prepared a double molecule of antipyrin, making diphenylmethylpyrazonyl and called it "rossium". He found that this would prevent death in a sensitized guinea pig that had received from four to five times the usual fatal dose of antigen. On the hypothesis that the morphinism was of allergic nature and that the withdrawal symptoms were those of anaphylactic shock, he tried the use of rossium for the prevention of the withdrawal symptoms of morphine. Of fifty-four new preparations which he made and tested for their ability to prevent anaphylactic shock in animals and for their effectiveness in addicts, Ostromislensky found that, although several would reduce the withdrawal symptoms of morphine, rossium was the one best adapted for this purpose. Clinically rossium has been found to be an excellent analgesic against intense pain of sciatica, and certain menstrual pains. Rossium also has a markedly soothing effect in asthma, which is often of allergic origin. As already mentioned, it quiets the intense nervousness following the alcoholic debauch and seems to shorten the excitement of delirium tremens. It would seem, therefore, to be not a specific against the withdrawal of morphine or against the different conditions here named. In all probability it has some action on the autonomic nervous system, acting either in a peripheral manner or on the parasympathetic or the sympathetic centers. The balance of the autonomic nervous system is upset during morphine withdrawal, for vomiting, purging, sweating and lacrimation are all symptoms of the overstimulated parasympathetic system. These are the symptoms which are greatly alleviated by the giving of rossium, but the apparent action of stimulation of the parasympathetic may in reality be an inhibition of the normal action of the sympathetic. Those two possibilities cannot be actually separated except by further experimentation. The action of rossium may possibly occur high up in the hypothalamus or in the medullary centers. There are no experimental data yet to prove which it is. It seems, however, most likely that the action of rossium is that of an analgesic on the sensory nerves of the sympathetic system. In some unknown way it preserves the usual equilibrium between the sympathetic and the parasympathetic. We cannot, today, go farther.

In 1928 the Mayor's Committee on Drug Addiction in New York City was appointed. This committee studied under carefully controlled conditions the action of the various recognized drugs believed to relieve the withdrawal symptoms of morphine. In giving the various treatments, a similar number of addicts were taken as controls. These controls were given no narcotics. Graphs were drawn of the intensity of the symptoms of the medicated and of the control patients. We, therefore, obtained a graph showing the symptoms of withdrawal of morphine without narcotics of any kind. This graph of 100 control patients can be used as an accurate comparison for any kind of treatment in the withdrawal of morphine; it remains a permanent record by which to judge other

treatments. Judging from this graph, it is evident that the untreated cases of narcotism from heroin or morphine, after an absolute abrupt withdrawal, will begin to yawn and feel weary, when their next dose would ordinarily come due. They begin to have indefinite pains and an uneasiness and nervousness which is indescribable, but very noticeable. After a few hours of this, they become nauseated, begin to have pain in the epigastrium with nausea and vomiting followed by a very active diarrhea, and have severe abdominal and muscle cramps. This lasts without relief, growing more and more intense at night, for the first twenty-four to thirty-six hours. The nervousness and fear increase to such an extent that it becomes a terrific dread of some undefined terror, which is worse and more alarming to them than the fear of death. The almost universal fear of death in humanity is also present and adds to their misery. The gastrointestinal symptoms increase in their intensity, reaching their height on the third or fourth day, then rapidly subside. The muscular discomfort is at its height also on the fourth day and then rapidly improves. The restlessness and psychomotor activity reach their height on the third day, and subside, and the prostration coincides with them. It was found that the use of narcosan, a treatment by injections of a lipoid protein, atropine, hyoscin, slow withdrawal of morphine and a seven or a fourteen day withdrawal of morphine did not prevent the occurrence of the withdrawal symptoms. Atropin diminished the gastrointestinal symptoms; hyoscin increased these symptoms and produced an active delirium with severe prostration and weakness. Slow withdrawal was a disagreeable nagging misery, much resented by the patients. The seven and fourteen day withdrawals delayed the certain occurrence of the withdrawal symptoms and slightly reduced their intensity. Codein was the only drug used which decidedly diminished the symptoms. I therefore, devised, as already published, a treatment consisting of increasing the amount of codein as one simultaneously reduced the morphine. The codein was increased up to 5 grains every four hours. After the morphine had not been given for four days, the codein was rapidly cut down in a four-day period. This was the most successful and the least painful of the methods I have used, but it requires a month to six weeks of hospitalization and sometimes ends with a codein habit to be reduced. The old belladonna hyoscyamus treatment I used so long is effective but depends after all on codein to relieve the second half of the treatment.

I have used rossium in some seventy-five patients for treatment of addiction to various opium alkaloids. I have also used it in many alcoholics. I have found that the treatment by rossium successfully reduces the withdrawal symptoms and the period of hospitalization more than any other.

Comparing the withdrawal symptoms under rossium with those under the other forms of treatment, it will be seen that by the method to be described, the gastrointestinal symptoms are reduced to a minimum. The muscular aches, joint pains and abdominal cramps can be controlled by glucose; the nervous restlessness and terrors can be controlled by small doses of codein. The difference of the picture compared with that of the graph of the controls is most striking.

The amount of rossium to be given is governed by the body weight of the patient. Multiply the body weight of the patient by .05 and one obtains the number of grams of rossium to be used in the twenty-four hours. If a patient weighs 120 pounds, the dose is 6 grams. This means two 0.5 gram capsules every four hours. This amount of rossium is accompanied during the first forty-eight hours by a sufficient dose of morphine to make the patient comfortable. There is no use in waking the patients between midnight and early morning, for most of them will sleep as long as they know they are not to be deprived of their morning dose. If they are accustomed to sleep the whole night through, it is wiser to give a larger dose of rossium at night and the first thing in the morning, in that way obtaining the desired number of grams of rossium in twenty-four hours without waking the patient. The first symptoms of rossium in some patients will be that they begin to perspire, but will feel perfectly comfortable as long as they have their morphine. At the end of about forty-eight hours, at midnight or at the time the patient usually goes to sleep, the last dose of morphine is given, but the rossium is continued. The patients, in that way, will sleep through the first night of their deprivation as usual and this somnolence may last through the following day. They must be wakened during the day, however, to obtain their rossium. After the first sixteen hours of deprivation the sweating will increase in intensity and the patient will begin to feel some aching discomfort. They will feel as if they had a slightly running nose and as if they were having a beginning attack of grip. In some patients there is a slight nausea. Some may have one or two movements of the bowels, but the diarrhea does not proceed beyond that. There may be slight vomiting, but it is not excessive. If nervousness and the apprehension appear and are pronounced, it is wise to give these patients either one half grain of codein every two or four hours or, if the apprehension and restlessness are quite marked, a grain can be given with impunity. It adds to their comfort and it stops any disagreeable symptoms; it does not in any way hinder the

withdrawal of the morphine, nor does it possess any danger of the acquisition of the codein habit. I have found useful the fact that each one of the opiates has its own length of time in which the habit is formed. During the withdrawal period the variation in these time schedules can be made a very useful means of playing one opiate against another to relieve the nervousness, insomnia or pain.

Codein is particularly valuable in getting a patient off of morphine, dilaudid or heroin. I have found in the withdrawal of codein that dilaudid is particularly useful and is better than morphine. I have also found, if codein does not act or has to be given in large doses to stop the fear and nervousness in the withdrawal of morphine, that dilaudid will control these symptoms and can be used without fear of its own habit in the four or five days that are necessary to help the patients in control of their discomfort. If the patients begin to have an aching of the muscles, disagreeable abdominal cramps and pains, the injection of glucose intravenously in a 25 or 50 per cent solution relieves them very quickly. This should be accompanied by the subcutaneous injection of about two-thirds of the equivalent units of insulin. In some sensitive patients, the rossium may cause a slight vomiting on the third or fourth day. If that is so, cut the dosage of rossium to one half.

If the patient is restless and cannot sleep, any hypnotics that will make him sleep can be used. If you desire to use the barbiturate group, those barbiturates which are quickly absorbed and quickly eliminated are the best. The carbamide hypnotics are very useful to soothe the restlessness. Chloral I find in these patients a very useful drug. It can be given in moderate doses, sometimes with bromides. Often in the period of withdrawal, the mixture of hyoscin, chloral and codein is very effective. There is one method of giving hyoscin that is very valuable and often this drug can be used as the only hypnotic with great benefit and success. It should be given in doses of 1/400th of a grain. It quiets their restlessness and gives sleep at night, but should be given only once or twice in twenty-four hours. Many people, however, are very sensitive to hyoscin and, if the patient shows a dryness of mouth and a distinct restlessness after the first dose, do not repeat it. Do not consider that the patient has not had enough; a great many patients, even with this small amount, have had too much. But some patients can take with benefit 1/600th of a grain or 1/800th of a grain. I have seen patients that even with a dose of 1/800th of a grain had a dry throat and a restless fear that prevented any use of hyoscin.

If patients cannot take the injections of glucose or if it is impractical to give it to them because of the smallness of their veins, orange juice, to which an abundance of lactose is added, furnishes the necessary carbohydrate to quiet their restlessness and pain and to improve their condition. Lactose is used here because it is much less sweet than the other sugars and can be taken in larger amounts. I have seen patients supply themselves with a jar of "jaw breakers" and constantly munch them during the day with a great deal of benefit. In the convalescence of the patient from withdrawal symptoms, it is wise to continue the sugar for a week or ten days, and to use the hyoscin to help them sleep. With several patients, in whom most of the hypnotics were found to be of little value and with whom it was possible to obtain good co-operation, I have told them that it was impossible to make them sleep, but that, if they would make up their minds that they could not sleep, would turn on the light and read an entertaining detective story or anything they chose to read and would do that for two or three nights, they would gradually regain their ability to sleep. If they could get over the idea that they must sleep, or that sleep made any difference to their health, they would soon obtain a beginning of their natural sleep, which would rapidly increase. This was most effective with the younger group of patients, those who were accustomed to late hours and to the realization that they could sit up most of the night amusing themselves without injury. If they could combine that idea with the fact that they had broken the habit of sleeping by their opiates, they would soon be able to sleep naturally. Many addicts have a firm conviction that they will die if they do not sleep and, of course, they are terrified. Such an idea is a psychologic prejudice difficult to overcome; but, if you persuade them that "it is easy enough to lie down and die but it's the going on living that's hard," you will often benefit them.

After the withdrawal of morphine, at odd intervals of one or two or three weeks there is in some patients, a return of a sense of nervousness, which may reach a disagreeable degree, and there may come with it a distinct desire for morphine. If we accept the allergic hypothesis, this may be due to an accumulation of antigen combining with the antibody, producing a slight flare-up of withdrawal discomfort. This can be controlled with a few small doses of codein. A 1/400th of a grain of hyoscin will quiet their restlessness. These periods do not last as a rule more than twenty-four hours and may not occur again. Some patients do not have the return of these periods; others may have them as late as forty or fifty days after they have been off their morphine.

When you have successfully obtained a withdrawal of morphine, do not for one minute think that you should apply the word "cured" to your patient. It is then that you must consider and actively treat the psychologic dis-

tortion of your patient, which forced him into morphinism. You will have to reconstruct him psychologically and physically, just the same as you would any worn out, unhappy patient. This is especially true of the psychogenic group. If you find that you are dealing with one of those primitive, unhappy personalities in which the intelligence does not control the emotions you will have a very difficult task. With your patients who have taken morphine because of pain, if you bring them through one, two or several of these annoying recurrences of nervousness and a flare-up of the desire, you can produce a successful cessation of their addiction and you will see a very happy patient.

In young patients a good thorough course of physical exercise and physical training is very valuable. As your whole basis for the treatment of many of these alcoholic and morphine patients is relief of distortion of emotions, necessitating a reorganization of their emotional life, you will find in those who have, by their training, a grasp of religious values a very valuable and powerful adjunct. To those who are not fortunate enough to possess this sense of values, there must be found some emotion higher and more powerful than the desire for obliteration of reality and the patient must be made to face existence. In professional men and in men in active life, it is the sense of their economic responsibilities and the fear of detection that will hold them. Among professional patients, where unfortunately a large number of physicians through sickness or exhaustion from overwork are caught in the toils of morphinism, the firm determination of the Government to eradicate the use of morphine among this class of patients is often of great value, through fear, to hold them in check. The patients in the psychopathic groups, of which the underworld addicts are so largely composed, should be under Government control, the same as the insane. The work at Lexington, Kentucky, seems to me as being most judiciously carried on and promises a very real success in the control of these patients. In discussing the morphinist and the alcoholic, I have given you a review of the results of a personal experience of over forty years with these patients. I have tried one treatment after another to improve the care and to diminish the intensely trying period of withdrawal of the opiates. I am offering you here tonight in the use of rossium, a new treatment. It is a new drug and, with it, a new hypothesis has been offered to explain the unsolved problems in the opiate habit. It remains for the future to decide whether this hypothesis remains a hypothesis or will be proved to be a fact.

MEDICAL PROGRESS

ADVANCES IN PEDIATRICS*

BY R. CANNON ELEY, M.D.†

Neonatal Mortality:

ONE of the most practical as well as important innovations that has recently been introduced as an aid in the reduction of infant mortality has been the employment of the roentgen ray (1) as a means of determining the size, i.e., weight, of the fetus. By this procedure the viability or nonviability of the baby from a physiological standpoint can be accurately determined prior to delivery. In pregnancies complicated by placenta praevia, toxemias, and heart disease, stereoroentgenometric examinations have proved of inestimable value in determining the "risk" for both the mother and the baby. There can be little doubt that the progressive reduction in neonatal mortality has been due to the decreased number of deaths occurring among prematurely born infants for it is in this group that one encounters such a high mortality rate. Clifford[1] has pointed out that "at the Boston Lying-in Hospital about three per cent of the 3000 deliveries per year result in the birth of premature infants—*yet this three per cent accounts for fifty per cent of the total* neonatal deaths." In view of the fact that the majority of deaths among the premature infants occurred within the first forty-eight hours of life, the records of 304 of these infants were critically appraised in an effort to determine the most effective means of approach in reducing this high mortality rate.

The results of these studies[1] have shown that the most dangerous method of delivery "is the present technique of Caesarean section which carries a mortality of 44.4 per cent." However, it appears that the administration of morphine to the mother within two to four hours before the delivery exerts more influence upon the infant, i.e., by depressing the respiratory center, than the operative procedure. In a study of 850 consecutive premature deliveries in which 752 of the mothers *did not* receive morphia within four hours of delivery, the infant mortality rate was 36 per cent as compared with 60 per cent infant mortality rate in the group of mothers who *did* receive the drug within this specified period of time. Clifford[1] has recently made a study of 120,726 consecutive deliveries

*From the Department of Pediatrics, Harvard Medical School, and Infants' and Children's Hospitals, Boston, Massachusetts.

†Eley, R. Cannon—Associate in Pediatrics and Communicable Diseases, Harvard University Medical School and School of Public Health. For record and address of author see "This Week's Issue," page 97.

occurring at the Boston Lying-in Hospital over a period of time extending from 1873 through 1935 and from this has been able to point out the various factors, as well as diseases, which influence the mortality statistics.

Acute Lymphocytic Choriomeningitis (Acute Aseptic Meningitis)

This syndrome, although previously described in 1926 by Wallgren,[2] received little if any attention in this country before 1929 at which time three cases were reported by Viets and Watts.[3] Subsequent to their reports, which they termed acute aseptic meningitis, there has developed a widespread interest in this syndrome.[4, 5, 6, 7, 8] Practically all of the cases of acute lymphocytic choriomeningitis reported have occurred among young adults.

The initial symptoms are similar to those of a respiratory infection. However, these are soon replaced by signs and symptoms which suggest the possibility of some infection of the central nervous system. The cerebrospinal fluid is usually under increased pressure, clear in appearance, or at the most, slightly hazy; quantitative determinations of the sugar, protein, and chloride content show them to be within normal limits; microscopic and cultural studies fail to reveal any organisms. Cytological examination shows a pleocytosis varying from 50 to 2000 cells, the majority of the cells being of the lymphocytic series. The course of the disease is usually of short duration, lasting from eight to fourteen days and as a rule without residual paralysis.

In the course of virus transmission studies on monkeys, Armstrong[10] encountered a virus that produced a train of symptoms in these animals closely simulating the clinical picture of "aseptic meningitis" in human beings. Traub[11] later isolated a virus from white mice which closely resembled the virus isolated by Armstrong, and recently a similar virus has been isolated from four cases by Rivers and Scott.[12] As subsequent immunological and serological studies have shown the virus isolated by these workers to be the same, it would appear that this type of encephalitis is a definite clinical entity and not related to the types of encephalitis previously described.

That there may be other virus diseases discovered seems likely, as Toomey[9] had the opportunity to observe and study seventy children who developed a train of symptoms simulating those seen in acute benign lymphocytic choriomeningitis within twenty-one days after the development of the first case. It would therefore appear that a number of similar clinical entities may easily be confused with lymphocytic choriomeningitis; particularly acute anterior poliomyelitis and tuberculous meningitis.

Gonorrheal Vaginitis:

In view of the observations of Allen[13], Lewis[14] treated eight children suffering from specific vaginitis with "theelin" and noted that the histological changes produced in the vaginal epithelium of the patients were similar to the changes produced experimentally in the vaginal epithelium of young monkeys. Associated with this change in the type of vaginal epithelium, the discharge disappeared and the causative organisms could no longer be demonstrated. These observations were soon confirmed by Brown.[15] Huberman and Israeloff[16] successfully treated five patients by subcutaneous injections, also good results were obtained by Reading[17] when the substance was given intramuscularly. Goldberg, Minier, and Smith[18] treated seventeen children suffering from vaginitis and of the sixteen cases with specific infection fourteen, or 87.5 per cent were considered as cured; no recurrences were noted after their discharge from the hospital. Phillips[19] treated thirteen girls, and six weeks after cessation of all treatment, 70 per cent of the patients "relapsed". The results obtained by Witherspoon[20], however, are in sharp contrast to those mentioned above, as this observer was unable to note any improvement in ten patients treated by the injection of amniotin.

Since it is recognized that "theelin" is a potent hormone, the question has naturally arisen as to whether the administration of this substance to young girls will prove to be harmful. Miller[21] who recently had the opportunity to perform a biopsy on the ovary of a child who had received 1100 rat units, was unable to demonstrate any abnormalities. Nabarro and Signy[22] observed hypertrophy of the breasts in one of their treated cases; the enlargement subsided with cessation of treatment. Witherspoon[20] speaks discouragingly of the occasional secondary sexual changes that may occur during treatment, while others have raised the question as to whether the pelvic hyperemia may not be conducive to an extension of the inflammatory process. An answer to this last objection may be found in a recent publication by Novak[23] who states, "the fear that pelvic hyperemia produced by estrogenic substances may predispose to uterine and tubal extension of the vaginal infection is probably more apparent than real". Although the reported results should not be considered conclusive, they are of such a nature as to warrant further observations.

Gonadotropic Hormones in the Treatment of Undescended Testes:

In 1930 Schapiro[24] treated thirteen patients with cryptorchism by the intramuscular injection of a gonadotropic hormone obtained from the urine of pregnant women and noted that

in all cases the testes descended into the scrotum more or less completely. Since that date similar results have been observed by Goldman and Stern,[25] Kunstadter and Robins,[26] Sexton,[27] Rubinstein,[28] Aberle and Jenkins,[29] Brosius,[30] Webster,[31] and Dorff.[32] Spence and Scowen[33] obtained satisfactory results in the treatment of eleven patients and have recently published observations on their previously treated cases (after cessation of treatment) and twenty-two additional cases.[34] Their results can best be stated in the following quotation: "Thirty-three patients, aged four to twenty-six years, with imperfectly migrated testes have been treated with the gonadotropic hormones of pregnancy urine (pregnyl) given in doses of 500 rat units intramuscularly twice a week. Both testes descended into the scrotum in six of the bilateral cases and one in four, while in two cases descent has not occurred. In eleven out of nineteen unilateral cases the testis descended, and in two cases with the testes high in the scrotum. Successful results were obtained within periods ranging from two weeks to fourteen and a half months. The testes have remained within the scrotum in nine out of eleven cases followed for one to eleven months after cessation of treatment."

As pointed out by Drake[35] the testes sometimes descend spontaneously and this fact alone makes it difficult to appraise the results obtained by hormone therapy. However, the age distribution in some of the patients treated by Spence and Scowen would contraindicate the possibility of a normal descent. From the literature it would appear that this form of treatment might be tried *before* surgical intervention is instituted *except* in those instances in which there is mechanical obstruction, and which naturally demand surgical care.

Meningitis:

Carey[36] has recently reported the occurrence of an unusual type of meningitis in a boy three years and eight months of age. This patient was admitted to the hospital on account of headache and delirium of one week's duration. Physical examination revealed a drowsy, stuporous child with temperature 102.8°F., pulse 130 per minute and respirations 25 per minute. The remainder of the examination was negative except for signs of meningeal irritation as evidenced by nuchal rigidity, exaggeration of the deep reflexes and a positive bilateral Kernig's sign. The laboratory studies were not unusual except for the examination of the cerebrospinal fluid. This fluid reflected the presence of a purulent infection of the central nervous system. However, cultures of the cerebrospinal fluid revealed the presence of a small gram-positive bacillus. For the following twelve days from 25 to 50 cc. of cerebrospinal fluid were removed each twenty-four hours and in the first six specimens of this fluid the same gram-positive bacilli could be demonstrated both by direct bacteriological examination of the fluid and by cultural methods. At the end of twelve days the patient made an uneventful recovery and was discharged from the hospital. Subsequent psychometric and physical examinations have shown no sequelae to the infection.

At first it was thought that the gram-positive bacillus was a member of the diphtheroid group. However, the morphological, cultural, and immunological relationships of this organism to other identified members of the Genus Listerella showed that it belonged to the latter group. Human infection with this type of organism is exceedingly rare. Schultz[37] in 1934 reported the recovery of a woman from whose cerebrospinal fluid a similar organism was recovered; during the same year Burn[38] reported the isolation of this type of organism from the cerebrospinal fluid of two fatal cases of meningitis in newborn infants. In 1935, Seastone[39] reviewed the literature concerning these varied human and animal infections and showed that all of the organisms reported could be classified under the Genus Listerella group. One of the characteristics of this organism is its agglutination to a significant titre in normal horse serum and this feature may be of diagnostic aid in identifying similar organisms found in human or animal infections.

Continuous Intravenous Therapy:

The therapeutic benefit derived from the continuous administration of solutions by the intravenous route has long been recognized in the treatment of surgical and medical conditions occurring among adults.[40, 41, 42, 43] However, it is only within recent years that this method of therapy has been applied satisfactorily to the practice of pediatrics. In the majority of instances its use in the latter group of patients has been confined to the administration of physiological salt solutions and glucose solutions rather than to the administrations of serums, antitoxins, dyes, etc. Karelitz,[44] and Karelitz and Schick[45] have reported excellent results following its use in the treatment of "alimentary toxicosis"; Stokes[46] has indicated its value in combating ketosis, and in stimulating renal function; Cohen[47] et al. have demonstrated its importance as a means of establishing normal acid-base equilibrium and Nesbit[48] has found it of distinct advantage as a preoperative measure in the treatment of children with upper intestinal tract obstruction. The largest series of patients treated by this procedure has been reported by Ashby and Moore.[49] These observers treated 511 cases with satisfactory results. This method of treatment is *not* without danger, as thrombosis, the introduction of sys-

temic infections, and the development of local inflammatory reactions may occur. Any vein may be employed for this procedure, such as the saphenous vein of the leg or the veins in the cubital fossa. In infants, and particularly the very young patients, the small venules and capillaries of the scalp are the vessels of choice as this site precludes the necessity of dissecting the vein, and will admit a needle which *per se* controls the proper rate of flow. Furthermore, the vessels are stable and there is less danger of the needle being displaced by the infant's activity. It is a good therapeutic measure which should not be placed in disrepute by its careless or indiscriminate application.

Vitamin C:

Although Szent-Györgyi[50] had previously isolated a strongly reducing substance from the adrenal cortex which he called hexuronic acid, it was not until the work of King and Waugh[51, 52] that its definite and final identification with vitamin C was established. Following their observations rapid advances in the study of the chemical nature of vitamin C were made with the result that it was soon obtained in the pure crystalline form, thus affording the means of determining its physiological functions and their clinical application. The recent publication of King[53] concerning its chemical nature and physiological properties is so complete that repetition is unwarranted. Coincident with this progress has been the understanding of the pathological processes encountered in clinical scurvy as described in the studies of Wolbach et al.[54, 55] and Park et al.[56] Other workers have elucidated many important and practical facts. For example, the knowledge concerning the effect of freezing,[57] drying,[58] canning,[59] cooking,[60] and storage[61] has made it possible to preclude the possibility of developing scurvy by the accidental destruction of the vitamin during the preparation of foods.

During the past few years many advances have been made in regard to the clinical importance of this vitamin. The knowledge that human beings cannot synthesize ascorbic acid has made it apparent that unless an adequate amount (25 mg. in infants and about 40 mg. in adults) is ingested daily there will be a gradual depletion of the body stores resulting in the development of clinical scurvy. This is of further importance in the pregnant mother, for it has recently been shown by Jackson and Park[62] that infants may manifest scurvy shortly after birth, which of course implies that during the period of gestation the mother's diet has been inadequate. Harris and Ray[63] have demonstrated that infants with a deficient vitamin C intake excrete less of this substance in their urine in response to a standard test dose, than do infants receiving an adequate amount and as a result of such studies it is now possible to obtain evidence of avitaminosis before it manifests itself in the usual clinical manner. Abt, Farmer and Epstein[64] have recently determined some normal values for reduced cevitamic acid in the blood plasma of infants and children, thus offering a method by means of which the nutritional state of the infant relative to vitamin C may be appraised at any time. These observers also pointed out the unreliability of single capillary skin resistance tests or chemical examinations of the urine as indicative of the total amount of vitamin C present in the blood plasma. Efforts have been made by Goettsch[65] to ascertain whether the administration of a single large dose of vitamin C is as effective for therapeutic purposes as the daily oral administration of small amounts. For this purpose four infants with severe scurvy were treated by the intravenous administration of cevitamic acid[66] and compared with a control group who received small amounts of orange juice orally. The results showed that calcification of subperiosteal hematomata occurred at an earlier date in the former group than in the latter. Furthermore, "a single massive dose of cevitamic acid given either in pure form or as orange juice appears to favor healing of infantile scurvy as effectively as would the same total dose given in several daily proportions over a period of eight days." Although the daily requirements of vitamin C have been established for the normal individual, as shown by the fact that quantities over the required amount are eliminated unaltered by the kidneys, yet it is quite probable that infectious conditions may be accompanied by an excessive loss of the substance from the body tissues.[67]

Hemophilia:

As a result of Sakurai's[68] observation that the action of placental "toxins" in reducing the coagulation time of recalcified blood plasma was similar to the action of animal tissue extracts,[69, 70, 71, 72] and the fact that certain writers had suggested that such extracts might possess a certain degree of specificity for the species from which they were obtained, Eley, Green, and McKhann[73] investigated the possibility of obtaining a blood coagulant extract from the human placenta. In vitro and in vivo studies have shown that such an extract obtained from the human placenta possesses a potent coagulant factor and that when given by mouth or intramuscularly will produce a rapid reduction in the coagulation time of both the capillary and venous blood. It *should never be given intravenously*, as in vivo studies have shown that when so administered the animals die from intravascular coagulation. Nineteen children suffering from hemophilia have

received the blood coagulant extract and in fifteen instances there has been a satisfactory response as evidenced by a reduction in the coagulation time of the venous blood to within normal limits. This reduction is only temporary and treatments have to be repeated. Older children and adults have proved more refractory. This work is still in the experimental stage of development and definite conclusions as to its value cannot be made at the present time.

REFERENCES

1. Clifford, S. H.: Surg. Gynec. & Obst. **58**:727 (April) 1934; Surg. Gynec. & Obst. **58**:959 (June) 1934; New Eng. J. Med. **210**:570 (March 15) 1934; J. Pediat. **5**:139 (Aug.) 1934; J. A. M. A. **103**:1117 (Oct.) 1934; West Virginia M. J. **31**:3 (Aug.) 1935; J. Pediat. **8**:367 (March) 1935.
2. Wallgren, A.: Wien. Arch. f. inn. Med. **12**:297 (Feb.) 1926.
3. Viets, H. R., and Watts, J. W.: J. A. M. A. **93**:1553 (Nov. 16) 1929.
4. Gager, L. T.: Virginia M. Monthly **57**:532 (Nov.) 1930.
5. Dickens, P. F.: U. S. Nav. M. Bull. **30**:362 (July) 1932.
6. Bloedorn, W. A.: M. Ann. Dist. of Columbia **1**:203, 1932.
7. Viets, H. R., and Watts, J. W.: J. Nerv. and Ment. Dis. **80**:253, 1934.
8. Findlay, G. M.; Alcock, N. S., and Stern, R. O.: Lancet **230**:650 (March 21) 1936.
9. Toomey, J. A.: J. Pediat. **8**:148 (Feb.) 1936.
10. Armstrong, C., and Lillie, R. D.: Pub. Health Rep. **49**:1019 (Aug.) 1934.
11. Traub, E.: Science **81**: 298 (March 22) 1935.
12. Rivers, T. M., and Scott, T. F. M.: Science **81**:439 (May 3) 1935.
13. Allen, E.: J. Morphol. **46**:479 (Dec.) 1928.
14. Lewis, R. M.: Am. J. Obst. & Gynec. **26**:593 (Oct.) 1933.
15. Brown, J.: J. A. M. A. **102**:1293 (April 21) 1934.
16. Huberman, J., and Israeloff, H. H.: J. A. M. A. **103**:18 (July 7) 1934.
17. Reading, B.: South. M. J. **28**:464 (May) 1935.
18. Goldberg, L. E.; Minier, C. L., and Smith, E. L.: J. Pediat. **7**:401 (Sept.) 1935.
19. Phillips, R. B.: New Eng. J. Med. **213**:1026 (Nov. 21) 1935.
20. Witherspoon, J. T.: Am. J. Dis. Child. **50**:913 (Oct.) 1935.
21. Miller, J. R.: Am. J. Obst. & Gynec. **29**:553 (April) 1935.
22. Nabarro, D., and Signy, A. G.: Lancet **1**:604 (March 16) 1935.
23. Novak, E.: J. A. M. A. **104**:1815 (May 18) 1935.
24. Schapiro, B.: Deutsche Med. Wchnschr. **56**:1605 (Sept.) 1930.
25. Goldman, A., and Stern, A.: New York State J. Med. **33**:1095 (Sept. 15) 1933.
26. Kunstadter, R. H., and Robins, L. S.: J. Pediat. **4**:774 (June) 1934.
27. Sexton, D. L.: Endocrinology **18**:47 (Jan.-Feb.) 1934.
28. Rubinstein, H. S.: Endocrinology **18**:475 (July-Aug.) 1934.
29. Aberle, S. B. D., and Jenkins, R. H.: J. A. M. A. **103**:314 (Aug. 4) 1934.
30. Brosius, W. L.: Endocrinology **19**:69 (Jan.-Feb.) 1935.
31. Webster, B.: J. A. M. A. **104**:2157 (June 15) 1935.
32. Dorff, G. B.: Am. J. Dis. Child. **50**:649 (Sept.) 1935.
33. Drake, C. B.: Quoted by Spence, A. W., and Scowen, E. F.: Proc. Roy. Soc. Med. **38**:427 (Feb.) 1935.
34. Spence, A. W., and Scowen, E. F.: Lancet **2**:1335 (Dec. 14) 1935.
35. Drake, C. B.: J. A. M. A. **102**:759 (March 10) 1934.
36. Carey, B. W., Jr.: In press.
37. Schultz, E. W.; Terry, M. C.; Brice, A. T., Jr., and Gebhardt, L. P.: Proc. Soc. Exper. Biol. & Med. **31**:1021 (May) 1934.
38. Burn, C. G.: Soc. Exper. Biol. & Med. **31**:1095 (June) 1934.
39. Seastone, C. V.: J. Exper. Med. **62**:203 (Aug.) 1935.
40. Hendon, G. A.: Ann. Surg. **91**:753 (May) 1930.
41. Hirshfeld, S.; Hyman, H. T., and Wanger, J. J.: Arch. Int. Med **47**:259 (Feb.) 1931.
42. Hyman, H. T., and Hirshfeld, S.: J. A. M. A. **96**:1221 (April 11) 1931; ibid., **100**:466, 1933.
43. Hyman, H. T., and Touroff, A. S. W.: J. A. M. A. **104**:446 (Feb. 9) 1935.
44. Karelitz, S., and Schick, B.: Am. J. Dis. Child. **42**:781, 1931.
45. Karelitz, S., and Schick, Béla: J. A. M. A. **99**:366 (July 30) 1932.
46. Stokes, J., Jr.: Pennsylvania M. J. **36**:421 (March) 1933.
47. Cohen, H.; Miller, P. R., and Kramer, B.: J. Pediat. **3**:299, 1933.
48. Nesbit, H. T.: J. Pediat. **1**:447 (Oct.) 1932.
49. Ashby, J. E., and Moore, H. L.: J. Pediat. **6**:88 (Jan.) 1935.
50. Szent-Györgyi, A.: Biochem. J. **22**:1387, 1928.
51. King, C. G., and Waugh, W. A.: Science **75**:357 (April) 1932.
52. Waugh, W. A., and King, C. G.: J. Biol. Chem. **97**:325 (July) 1932.
53. King, C. G.: Physiol. Rev. **16**:238 (April) 1936.
54. Wolbach, S. B., and Howe, P. R.: Arch. Path. **1**:1 (Jan.) 1926.
55. Menkin, V.; Wolbach, S. B., and Menkin, M. F.: Am. J. Path. **10**:569 (Sept.) 1934.
56. Park, E. A.; Guild, H. G.; Jackson, D., and Bond, M.: Arch. Dis. Child. **10**:265, 1935.
57. Nelson, E. M., and Mottern, H. H.: Indust. & Engin. Chem. **25**:216 (Feb.) 1933.
58. Yarusova, N.: Problems of Nutrition (U. S. S. R.) **3**:42, 1934.
    Morgan, A. F.: Am. J. Pub. Health **25**:328 (March) 1935.
59. Parsons, H. T., and Horn, C.: J. Agr. Res. **47**:627 (Oct. 15) 1933.
60. Newton, C. L.: Ga. Agr. Exper. Sta. Bull. **167**:3, 1931.
61. Isham, P. D., and Fellers, C. R.: Mass. Agr. Exper. Sta. Bull. **296**:2, 1933.
62. Jackson, D., and Park, E. A.: J. Pediat. **7**:741 (Dec.) 1935.
63. Harris, L. J., and Ray, S. N.: Lancet **1**:71 (Jan. 12) 1935.
64. Abt, A. F.; Farmer, C. J., and Epstein, I. M.: J. Pediat. **8**:1 (Jan.) 1936.
65. Goettsch, E.: Am. J. Dis. Child. **49**:1441, 1935.
66. Schultzer, P.: Lancet **2**:589 (Sept. 9) 1933.
67. Faulkner, J. M.: New Eng. J. Med. **213**:19 (July 4) 1935.
68. Sakurai, K.: Sei-I-Kai M. J. **48**:52, 1929. (Eng. Abstr.)
    Hori, E., and Sakurai, K.: Sei-I-Kai M. J. **49**:21, 1930. (Eng. Abstr.)
69. Wooldridge, L. C.: On the Chemistry of Blood and Other Scientific Papers. London. 1893.
70. Loeb, L.: Montreal M. J. **32**:507, 1903; Virchows Arch. f. path. Anat. **176**:10, 1904; Beitr. z. chem. Phys. u. Path. **5**:534, 1904; ibid. **9**:201, 1907; Ztschr. f. Immunitätsforsch. u. exper. Therap. **12**:189, 1912.
    Loeb, L., and Fleisher, M. S.: Biochem. Ztschr. **28**:169, 1910.
    Loeb, L.; Fleisher, M. S., and Tuttle, L.: J. Biol. Chem. **51**:461, 1922.
71. Howell, W. H.: Am. J. Physiol. **31**:1 (Oct. 1) 1912.
72. Mills, C. A.: J. Biol. Chem. **40**:425, 1919; ibid. **46**:135, 1921; ibid. **46**:167, 1921.
    Mills, C. A., and Guest, G. M.: Am. J. Physiol. **57**:395 (Oct. 1) 1921.
    Mills, C. A., and Mathews, S.: Am. J. Physiol. **60**:193 (March) 1922.
    Mills, C. A.; Dorst, S. E.; Mynchenberg, G., and Nakayama, J.: Am. J. Physiol. **63**:484 (Feb.) 1923.
    Mills, C. A.: Am. J. Physiol. **76**:651 (May) 1926.
73. Eley, R. C.; Green, A. A., and McKhann, C. F.: J. Pediat. **8**:135 (Feb.) 1936.

DEFECTIVE VISION DUE TO TOBACCO AND ALCOHOL

As a rule, neither tobacco nor alcohol directly affects the eyes, unless they have first attacked the general health, it is pointed out by Dr. Emanuel Krimsky, of Brooklyn, N. Y., answering some of the questions which are most frequently asked by patients, in a recent issue of *The Sight-Saving Review*, quarterly journal of the National Society for the Prevention of Blindness (Summer, 1936).

"And yet," says Dr. Krimsky, "every eye specialist in every book on eye diseases, gives prominent mention to blindness of varying degrees of severity from the prolonged and excessive use of either tobacco or alcohol in certain susceptible persons. It is extremely important to recognize blindness from tobacco or alcohol because immediate and complete abstention will often restore vision, unless the case has progressed too far. Wood alcohol blindness is permanent and cannot be cured."—*Bulletin, National Society for the Prevention of Blindness.*

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 22281

PRESENTATION OF CASE

First Admission. A fifty year old native plasterer was first admitted complaining of abdominal pain.

For two years the patient had been troubled by vague epigastric discomfort occurring about three hours after meals and usually relieved by a glass of milk. For about three weeks this discomfort was somewhat more severe than previously but was relieved by a liquid medication given by a local physician. On the morning of entry shortly after arising he was suddenly seized with violent cramp-like pain in the upper abdomen sufficiently severe to cause him to double up. He went to bed immediately and noted a dull aching pain in his left shoulder. A short time later the initial pain had spread over the entire abdomen but was most severe in the right upper quadrant. The pain was constant and was not associated with emesis or other evidence of bowel disturbance.

Physical examination showed a well-developed man lying in bed with his knees drawn up suffering from considerable abdominal pain. The skin and mucous membranes were dry and the heart and lungs were negative. The abdomen was flat and showed a diffuse board-like rigidity. There was marked generalized tenderness, more pronounced on the right side and in the upper midabdomen. Peristaltic sounds were absent. Rectal examination showed tenderness over the entire pelvic floor.

The temperature was 98°, the pulse 92. The respirations were 20.

Examination of the urine was negative. The blood showed a white cell count of 16,000.

Shortly after entry a perforation of the anterior surface of the stomach near the lesser curvature at the junction of the middle and lower thirds was sutured. On the second postoperative day the patient developed a temperature of 103° and signs considered significant of right lower pulmonary collapse. An x-ray examination showed this region to be involved by what was more probably a pneumonic process. Subsequently he improved considerably and on the fourteenth hospital day a gastrointestinal x-ray showed a markedly dilated stomach containing considerable fluid. Barium could not be forced through the pylorus and the antrum appeared markedly contracted. Two weeks later, having had symptoms of obstruction, a posterior gastrojejunostomy was performed. The region of the pylorus was not explored because of adhesions. In the mid-portion of the pancreas a hard nodular tumor was felt. Biopsy from this showed adenocarcinoma. The patient responded well postoperatively and was discharged on the forty-fourth day after entry.

Second Admission, four days later.

The patient returned without further symptoms for additional surgical treatment.

Physical examination showed no abnormality other than the healed scars of the two previous operations. On the second day a Billroth II was performed, the stomach being resected distal to the pre-existing gastrojejunostomy. Further, the spleen and all of the pancreas except for the proximal 1.5 centimeters lying within the curve of the duodenum were removed. Several enlarged firm lymph nodes in the region of the pancreatic tumor were likewise resected. Postoperatively the temperature rose to 103° and the patient was quite ill. He reacted promptly, however, improved rapidly, and was discharged on the seventeenth hospital day.

Third Admission, twenty-three days later.

Following his discharge the patient adhered rigidly to a special diet and his weight increased from 110 to 120 pounds. There was considerable gaseous eructation and passage of flatus but no epigastric discomfort. About a week after leaving the hospital he began to have attacks of dull aching pain at the right costovertebral angle occurring about five times daily and lasting about 5 to 15 minutes. It varied in severity and occasionally awakened him from his sleep. It was frequently relieved by lying upon the affected side or by evacuating stool or urine. It was always relieved, however, within five minutes after drinking a glass of milk. There were no other significant symptoms.

Physical examination showed no essential general change. The abdomen was spastic over the entire upper portion and to a lesser degree in the right lower quadrant.

The temperature, pulse and respirations were normal.

Examination of the urine was negative. The blood showed a red cell count of 2,500,000, with a hemoglobin of 50 per cent. The white cell count was 15,800, 72 per cent polymorphonuclears. A stool specimen gave a 4+ reaction to the guaiac test. A gastric analysis showed a free acid of 20 units and a total acid of 33. A

guaiac test upon the gastric contents was negative.

A gastrointestinal series showed a postoperative stomach with a gastroenterostomy. There was a large filling defect with sharp outlines, measuring 6 by 6 centimeters, involving the remaining portion of the antrum and the adjacent portion of the stoma. The rugae in the area of the defect were completely disorganized. Another x-ray study showed the same essential findings. The kidneys were normal in size and position and there were no unusual soft tissue masses. A small air-filled stomach was visualized and showed a soft tissue mass protruding from the medial side into the lower end of the gas-filled portion.

On the day after entry the patient began to vomit blood. Constant gastric drainage was instituted and he was given a transfusion. He improved gradually and was discharged on the fifteenth day.

Fourth Admission, twenty days later.

Since his discharge the patient had dull, gnawing, nonradiating epigastric pain. This was invariably relieved by sodium bicarbonate. His appetite was good and he continued to gain weight. The stools were tarry in appearance, but he was taking iron medication for his anemia. He also had some low back pain unaffected by motion but somewhat relieved by micturition.

Physical examination was unchanged.

Examination of the urine showed a slight trace of albumin but was otherwise negative. The blood showed a red cell count of 3,370,000, with a hemoglobin of 60 per cent. The white cell count was 13,900, 82 per cent polymorphonuclears. A gastric analysis showed a free acid of 42 units and a total of 57. After ergotamine the free acid was 70 and the total acid 80.

Another x-ray examination showed a Billroth II stomach with gastroenterostomy stoma about 6 centimeters proximal to the end of the stomach. The opening of the stoma was narrow at the beginning of the examination and only small amounts of barium trickled through it. Later this increased and eventually there was no delay in emptying. A pocket of the anastomosed jejunum was opposite the opening and the stomach above the stoma showed a hypertrophic gastritis. Below the anastomosis the stomach exhibited a well-defined ovoid defect. Rugae in the stomach in the region of the anastomosis were markedly thickened and both the stomach and adjacent jejunum exhibited a decrease of normal elasticity. There was slight decrease in size of the gastric defect since the previous examination. The chest and spine demonstrated no significant changes. The patient was discharged two days later.

Final Admission, two months later.

After leaving the hospital the patient continued his dietary régime and felt quite well although he continued to look pale. About a month before returning he began to have constant and gradually increasing pain in the region of his operative scar. This disappeared on the morning before re-entry and shortly afterward he vomited about four cupfuls of blood. Thereafter he became delirious and did not respond to any questioning. His condition remained unchanged up to his admission. There was no further hematemesis and his bowels did not move.

Physical examination showed a pallid, thin man with gasping respirations. He was somewhat stuporous and did not respond to questioning. The blood pressure was 100/50. The heart and lungs were negative. The abdomen was tense but there was true spasm only in the right abdomen and flank. Peristalsis was present.

The temperature was 99°, the pulse 120. The respirations were 20.

The nonprotein nitrogen of the blood was 48 milligrams and the blood chlorides were equivalent to 107 cubic centimeters of N/10 sodium chloride. The CO_2 combining power was 59.6 volumes per cent and the serum protein 4.1 grams.

While in the hospital the patient exhibited alternating periods of stupor and excitement. He was given supportive treatment and several transfusions, but failed to respond and died on the day following his final entry, seven months after his initial admission.

Differential Diagnosis

Dr. Arthur W. Allen: This fifty year old man was admitted to the hospital with a perfectly typical story of perforated peptic ulcer. He had had symptoms for three years that were pretty characteristic and it does not state in the record here how many hours he had been perforated when he came to the hospital. He was operated on very soon after admission and an ulcer in the anterior wall of the stomach near the lesser curvature was found perforated and this was sutured. He made a moderately good immediate convalescence but two weeks later began to show signs of stricture at the pylorus and began to vomit his food. At that time x-ray was made showing that he had a total occlusion at the pylorus. Two weeks after that he was operated on again. At this time he had a gastroenterostomy performed rather high on the posterior wall of the stomach. The surgeon who operated on him noted a firm nodule in the pancreas which was biopsied and an immediate diagnosis of adenocarcinoma was returned by the pathologist. It does not say whether it was adenocarcinoma of the pancreas or whether it was metastatic disease from the stomach. Although that is undoubtedly known it is not in the record. It was felt by the man

who operated on him undoubtedly that there was some chance of resecting this lesion at a later date, so that after a rather stormy convalescence from the gastroenterostomy he went home, forty-four days after his entry. He returned four days afterwards. He undoubtedly had gone home to get his affairs in order and came back for this third and more serious operation.

At the third operation he had his stomach transected distal to the enterostomy and had the diseased portion of the stomach removed, probably including the pylorus. The duodenal stump was turned in, leaving, with the previous anastomosis, a situation which we speak of as a Billroth II resection. At this time also his spleen and all of the pancreas except the proximal 1.5 centimeters were removed. With the pancreas and the tumor that was in it there were some lymph nodes around it that were removed as well. These lymph nodes are described as being very firm to palpation and were undoubtedly considered by the surgeon to be metastatic malignancy. This brings up a good many interesting points. The question of taking out the pancreas has recently come into vogue for various reasons. We have no hesitancy in taking out the head of the pancreas and the ampulla of Vater and so forth in carcinoma of the ampulla of Vater. Whipple and Parsons in the Presbyterian Hospital in New York have had three or four such successful operations. The gallbladder is first anastomosed to the stomach and the common duct ligated, and at the second operation you can go in and remove the head of the pancreas and the diseased portion of the duct. This shows that the individual can do perfectly well without pancreatic secretion. In other words, on a low fat diet a patient may do reasonably well. If any pancreatic tissue is left at all no insulin is needed. Recently the pancreas has been removed in a good many instances—not total removals but partial resections—for adenoma of the islands of Langerhans in individuals having symptoms of hyperinsulinism.

The reason the spleen was removed with the pancreas in this case was probably to make it technically more simple. Every once in a while in a gastrectomy it is easier to take the spleen out than to separate it from the fundus of the stomach. The spleen was undoubtedly small and the vessels that run through the pancreas are rather difficult to separate without damaging the blood supply to the spleen and undoubtedly it was removed not because it was diseased but because it made the operation easier and safer. He had a stormy convalescence after this large operation but he survived and was discharged seventeen days after the operation was done. He came back to the hospital twenty-three days later.

"About a week after leaving the hospital he began to have attacks of dull aching pain at the right costovertebral angle occurring about five times daily and lasting about five to fifteen minutes." The fact that this pain was relieved by various methods makes it a little difficult to say to what it might have been due. The fact that it was always relieved by a glass of milk would indicate that he very likely had a new ulcer in the stomach or in the jejunum that had developed since his last operation. The pain is not particularly characteristic so far as localization is concerned but it is possible to have ulcer pain radiate to the right costovertebral angle; also, it may have a deeper significance, as we shall see later on in the history.

"The blood showed a red cell count of 2,500,000, with a hemoglobin of 50 per cent." In other words this man had been bleeding from some source.

"A stool specimen gave a 4 plus reaction to the guaiac test." That without doubt indicates that he has bleeding from the gastrointestinal tract. The fact that the guaiac test on the gastric contents was negative is of no importance whatever. If the gastroenterostomy was open you might have had one negative guaiac quite easily.

He had at this time a gastrointestinal series. I wish we could see these plates and have them interpreted because it would make a good deal of difference in the diagnosis. They describe a filling defect in the remaining portion of the antrum of the stomach. One would suppose that all the antrum was removed at operation. They also state that the rugae in this area were completely disorganized. I think that would mean that this was an intrinsic lesion that developed in the stomach rather than something that was pressing on it from without.

I am sorry Dr. Holmes is not here. We will have to accept the gastrointestinal series as it is printed here, and here is one of the films. I would not dare try to interpret this picture but I agree that this may represent the gastroenterostomy with a little barium filtered out into the jejunum, the duodenum having been sutured off at this point; and I should suppose this area would be the lesion that has been described.

This gastroenterostomy opening has almost shut down. This is rather characteristic of gastroenterostomy in carcinoma of the stomach. It becomes occluded very rapidly by the encroaching disease to a point where a great many of us feel that gastroenterostomy in carcinoma of the stomach is hardly worth while because obstruction occurs again so rapidly. We have, however, definite evidence of hypertrophic gastritis and the stomach showed a "well defined ovoid defect". "There was slight decrease in the size of the defect since the previous examina-

tion." That would have to mean that it was ulcer and not cancer because cancer does not decrease under any circumstances, so far as the defect is concerned, and ulcer very often does.

Now to sum up the last admission. It says that he was pale and thin so we assume that he had lost a great deal of weight since the previous admission. He undoubtedly had had a good deal of trouble maintaining his nourishment, either due to the fact that the gastroenterostomy opening was being encroached upon from within or from without, and he was bleeding. We find at this admission that although he had spasm in the abdomen peristalsis was present, which I think probably rules out perforation of the remainder of the stomach and a peritonitis with it. His nonprotein nitrogen was elevated. His chlorides were within normal limits. His CO_2 combining power was a little high and the serum protein very low, a dangerously low level. The one criticism that I have in the last paragraph is that he had several transfusions. I think this is one of the typical examples of the abuse of transfusion. It seems like a terrific waste of blood to pour it into an obviously moribund man.

To go over the summary of the entire question, this man started with a perforated gastric ulcer that later caused pyloric obstruction requiring gastroenterostomy with an accidental finding of adenocarcinoma involving the pancreas. Later on they did a resection of the pancreas and resection of the distal portion of the stomach. The question is was this a carcinoma of the stomach with secondary involvement of the pancreas or was it an ulcer of the stomach all the time, and carcinoma primary in the pancreas which later recurred and finally was the cause of his death? Or was it carcinoma of the stomach in spite of this acidity, and did it finally recur in the stomach in a short period and encroach on the gastrojejunostomy causing obstruction with bleeding and death?

Dr. Tracy B. Mallory: We did not want to make any mystery of this portion of the story, Dr. Allen. We found a well localized nodule of tumor 3 by 2.5 by 7 centimeters in almost exactly the midportion of the pancreas. There was great dilatation of the ducts of the pancreas behind the tumor, and it was obviously obstructing them. There was no question in our minds that it was a primary carcinoma of the pancreas.

Dr. Allen: That helps a good deal. I think we may assume that this lesion in the stomach was not primarily cancer of the stomach but was ulcer and that this man probably had mechanical difficulty with his new opening, partially from the ulcer in his stoma, and it is possible that he did not have any recurrence of his pancreatic cancer. I believe, however, that he did have a recurrence of his pancreatic cancer, and that the probabilities are at autopsy we will find that that was true.

There is one point that might have been important that was not brought out and that is whether there were any metastases in the pelvis which could be felt by rectum. I think in the final stages that might have been ascertained. The fact that pain radiated through the back would not help us a great deal, because if the pancreas was involved by ulcer it might radiate through the back. I believe that this man had recurrence of his pancreatic carcinoma and that the lesion in the stomach was primarily ulcer and gastritis.

A Physician: What was the cause of the obstruction?

Dr. Allen: That I think was probably more from pressure without than disease within.

Clinical Diagnoses

Perforated perigastric abscess with ? peritonitis.
(Carcinoma of pancreas—Pancreatectomy.)

Dr. Arthur W. Allen's Diagnoses

Carcinoma of the pancreas with recurrence.
Gastritis.
Gastrojejunal ulcer.
Gastrointestinal hemorrhage.

Anatomic Diagnoses

Carcinoma of the body of the pancreas with metastases to the regional lymph nodes and to the liver.
Gastrojejunal ulcer.
Pulmonary edema, bilateral, marked.
Pleuritis, chronic fibrous, left.
Pleural effusion, slight, bilateral.
Pericarditis, chronic adhesive.
Operative wounds: Suture of the pylorus, resection of body and tail of the pancreas, splenectomy, posterior gastroenterostomy.

Pathologic Discussion

Dr. Mallory: I am sorry Dr. Churchill is not here to discuss this case. He performed most of the operations and found by accident a very small and apparently well circumscribed tumor directly in the body of the pancreas. There were about four small nodes involved in the immediate neighborhood but the tumor at the time of the first operation seemed so well circumscribed that he felt it worthwhile making an attempt at resection. The spleen was taken out, as Dr. Allen suggested, because it made the operation technically simpler and also because three of these involved nodes lay immediately around the splenic vein so that it would have been virtually impossible to dissect out the vein and be sure that you were not leaving tumor behind. The splenic vein on occasions is completely encased in pancreatic tis-

sue and is very often approximately two-thirds or three-fourths surrounded by the body of the pancreas. The complication which was the immediate cause of this man's death was a large gastrojejunal ulcer nearly 8 centimeters in diameter. The tissues around this ulcer were very markedly swollen with an inflammatory process, showing that there probably was an element of pressure from without in producing the obstruction. The pancreatic tumor had not recurred locally but at the time of autopsy we found three other lymph nodes higher up in the posterior retroperitoneal tissue and also a fine studding of small fresh metastases in the liver.

DR. ALLEN: I wonder if any of the internists can tell us whether this fat free diet was a poor ulcer diet.

DR. GERALD BLAKE: If you can keep up the nutrition sufficiently with fat free diet, as happened here, I do not think it is a bad diet. You depend on fat a good deal in an ulcer diet but it takes support away from you. I think a fairly satisfactory ulcer diet can be made without using fat.

DR. MALLORY: The final terminal event was hemorrhage into the bowel. We found the entire intestinal tract completely full of fresh blood. The last hemorrhage had gone downwards instead of upwards.

DR. ALLEN: Could you make out a large vessel that was eroded?

DR. MALLORY: No, we did not find any single vessel.

DR. ALLEN: The only other fatal hemorrhage from a gastrojejunal ulcer that I know about is one that had become attached to the middle colic artery and finally eroded into it so that patient died of a profuse hemorrhage.

CASE 22282

PRESENTATION OF CASE

A thirty-eight year old white native prison inmate was admitted complaining of sweating and fever.

The patient, serving an eight year prison sentence, had been well until about five weeks before entry when he was suddenly seized with a severe shaking chill which was followed by fever and profuse sweating. On three subsequent days he had further rigor but thereafter had none. He was confined to bed at the prison infirmary where he remained until his admission. Up to two weeks before entry he had a gradually rising fever in the morning which subsided toward evening. There were, however, profuse night sweats and progressive weakness. Two weeks before entry the fever rhythm changed and he had an evening fever of 104° and 105° with a morning temperature of about 96°. He had lost some weight, developed anorexia, and became slightly weaker. Otherwise he felt that there was no marked change in his condition since the beginning of his illness. There was some frontal headache, moderate polydipsia, and a slight cough productive of a small amount of mucoid material but no other associated symptoms. He had been given a course of quinine therapy without effect. On several occasions just before entry macroscopic hematuria was noted.

The past history is noncontributory.

Physical examination showed a well developed and nourished man with a rather fixed expressionless facies and hot dry skin. The eyes were slightly prominent. The right eyelid was a little puffy and the right pupil slightly irregular. The tongue was heavily coated and the breath had a foul odor. Oral hygiene was poor. The heart was not enlarged. The sounds were of poor quality but no murmurs or irregularities were audible. The blood pressure was 106/58. There was slight dulness at the right base posteriorly with slightly diminished tactile fremitus and breath sounds, but the lungs were otherwise clear. The abdomen was slightly distended and tympanitic. No evidence of fluid was elicited. The liver and spleen were not felt although the former seemed enlarged to percussion. There was moderate edema of the ankles and some coarse tremor of the extremities.

The temperature was 104.4°, the pulse 110. The respirations were 20.

Examination of the urine was negative. The blood showed a red cell count of 3,600,000, with a hemoglobin of 70 per cent. The white cell count was 7,400, 68 per cent polymorphonuclears, 22 lymphocytes, 3 monocytes, 6 myelocytes, and 1 nucleated red blood cell. There were polychromatophilia, anisocytosis, and many stippled red blood cells. No parasites were seen. The sputum was mucopurulent in appearance, and on one occasion contained blood but was otherwise negative. Stool examinations were negative. A Hinton test was negative. The serum protein was 4 grams. Agglutination tests for organisms of the typhoid group and undulant fever were negative. The blood chlorides were 100 and an icterus index was 3. Blood, stool and urine cultures were negative. A tuberculin test was negative.

X-ray examination of the chest showed shallow costophrenic angles and irregular diaphragmatic outlines. There was slightly decreased radiance in the right cardiophrenic angle, and the lung markings in other portions of the lung were slightly increased. The heart lay transversely and was not evidently enlarged. Hilar shadows were wide but no glandular masses were visible. A flat film of the abdomen showed calcified glands overlying the right ilium and evidence of metallic material in the buttocks.

The right kidney was normal but the left was incompletely outlined and its lower pole appeared enlarged. A pyelogram showed a normal right kidney but the left was obscured by gas in the colon. Intravenous dye, however, appeared promptly on both sides and demonstrated normal urinary passages.

The patient's condition continued relatively unchanged. His temperature remained elevated between 102° and 104° but his white blood cell count did not rise above 9,000. He gradually developed increasing edema as his serum protein dropped to 3.2 grams. Signs of fluid accumulation appeared at both bases and in the abdomen. On the ninth day 60 cubic centimeters of cloudy yellowish fluid was removed from the abdomen. The fluid had a specific gravity of 1.010 with a cell count of 60, most of which were lymphocytes. On the following day 50 cubic centimeters of straw-colored fluid was removed from the left chest. The fluid had a specific gravity of 1.006 and formed a pellicle. Thirty-six white blood cells were present, practically all of which were lymphocytes. On the thirteenth day he was obviously weaker. He became irrational and showed a respiratory rate of 50. The left pupil was pinpoint in character and did not react to light. The right pupil was negative. The fundi showed blurring of the nasal side of the discs and a few fresh hemorrhages. A lumbar puncture exhibited an initial pressure of 230 with normal dynamics. The cell count was 6 polymorphonuclears and 4 lymphocytes. Alcohol and ammonium sulphate tests were positive. He became rapidly worse and died on the following day.

Notes on the History

Dr. James H. Townsend: I take it that his maximum temperature was a little higher each day and reached its peak in the morning.

"There was slight dulness at the right base posteriorly with slightly diminished tactile fremitus and breath sounds, but the lungs were otherwise clear." In other words, a suggestion of a small amount of fluid in the right chest, or thickened pleura.

The respirations were only 20 in spite of the high fever, which strongly suggests that the trouble was not in the chest.

"Examination of the urine was negative." That is interesting in view of the fact that on several occasions he had macroscopic hematuria. I take it that several urine examinations were made and all were negative, no albumin, no pus and no blood found at any of the examinations.

According to the blood counts there was only a slight degree of anemia, of the secondary or hypochromic type. The smear of his blood evidently showed much more disturbance than one would guess from the counts alone. The myelocytes are interesting to note. One wonders what the nature of the sixty-eight per cent polymorphonuclears was, whether there was a high percentage of band forms with those and the myelocytes were just a slightly increased degree of the same thing, or whether the polymorphonuclears were of more adult character.

Dr. Tracy B. Mallory: There is a great deal of difference of opinion in regard to that blood smear. I wonder if the house officers care to speak up.

Dr. Robert F. Watson: I think the last one done by Dr. Stewart is the correct one. It shows a higher percentage of immature cells.

Dr. Townsend: Evidently there was a good deal of disturbance in the red cell marrow because there was active regeneration as shown by polychromatophilia and many stippled cells.

I take it that the sputum was never large in amount, just a small amount of blood-streaked sputum.

"The serum protein was 4 grams." In other words a great deal of loss of body protein as a result of febrile disturbance and we can account for the edema on that basis.

I should like to ask at this point if there were many blood cultures and if they were done with the ordinary media or whether there were special blood cultures done on special media to pick up a rarer type of organism?

Dr. Watson: Three blood cultures were taken. The pleural and abdominal fluids were also cultured, the latter both aerobically and anaerobically, and the urine and stools were examined. The bacteriologist was specifically asked to look for Brucella abortus.

Dr. Townsend: "A flat film of the abdomen showed calcified glands overlying the right ilium and evidence of metallic material in the buttocks." The only explanation I can offer for that is that at some time someone thought he had lues and he was treated with bismuth. At the present time his Hinton is negative but he may have had enough treatment to render that negative. That is suggestive evidence, however, that he may have had lues.

Would Dr. Holmes like to show us the x-rays at this point?

Dr. Holmes: I do not see any reason to change the interpretation at all from the way it is stated. Possibly there is a small amount of fluid present. Another finding that was not mentioned is that the left diaphragm is as high as the right, normally it should be a little lower.

Dr. Townsend: The lung fields were pretty clear.

Dr. Holmes: Yes.

Dr. Townsend: An old tuberculous gland. Is that the metallic material?

Dr. Holmes: I think that must be it. It is not very clear.

The intravenous injection does not fill the kid-

ney pelves and calices completely and you should not accept the findings as negative evidence. As far as we can make out the function is all right, but deformed calices could be missed.

DR. TOWNSEND: Does that show metallic material on both sides?

DR. HOLMES: Yes. I think that your observation is correct. He had had some metallic injections.

DR. TOWNSEND: The x-rays confirmed the presence of fluid in the chest and otherwise did not contribute very much directly.

The character of the fluid is that of a transudate, low gravity, very few cells, and, what there were, lymphocytes.

The fluid from the chest showed a gravity of 1.006 and formed a pellicle. Essentially the same character of fluid as from the abdomen except that it formed a pellicle. They do not say it clotted, however, and I should assume from that again that it was transudate due to chemical disturbance rather than exudate from an inflammatory process.

DIFFERENTIAL DIAGNOSIS

We are dealing with a febrile illness of seven weeks' duration. The patient ran a septic type of temperature the whole time and progressively became worse until the time of his death. The picture is that of a general septicemia of some sort but practically all the evidence that we have as to the nature of the infection, if it is an infection, is of a negative character. I think the best lead that we have as to the nature of the disturbance is what appears near the end of the history, the fresh hemorrhages in the retina. That is strongly suggestive of an embolic phenomenon and gives us the cue that this very likely might have been bacterial endocarditis.

Is there any other evidence of embolic phenomena to go with it? Back in the present illness on several occasions just before entry he had macroscopic hematuria. I think that is suggestive that he might have had infarcts in the kidney repeatedly, and at each time passed some blood. That however is not confirmed by the finding of blood while he was in the hospital. Then again just before he died there is a suggestion of something intracranial. Something happened rather suddenly, he became irrational, had a very high respiratory rate which again in the absence of a chest condition suggests something intracranial. He also had disturbance of the left pupil, a little increase in the pressure in the spinal fluid and slight blurring of the discs in addition to the hemorrhages All that, I should try to interpret on the basis of embolism, intracranial, with increased pressure and some reaction resulting in the slightly increased cell count in the spinal fluid and increased protein. Aside from that, we have very little except the various negative findings which tend to rule out such conditions as typhoid and undulant fever. We have no direct evidence of a heart disturbance in spite of the duration of seven weeks, which is not very long for malignant endocarditis. There were no murmurs to be heard but that does not absolutely exclude the diagnosis. Neither have we good evidence for any previous cardiac disease, which we should like to have for a diagnosis of malignant endocarditis, except possibly lues. He also had no enlarged spleen, at least not palpable, and nothing suggestive of other emboli, such as in the fingers. The blood disturbance is consistent with that diagnosis but there is nothing absolutely characteristic about it, such as the presence of phagocytic cells. The anemia, the level of the white cell count and the various disturbances of the red cells and white cells are, I think, consistent with that diagnosis.

What other conditions could possibly have caused such an illness? Perhaps one should consider tuberculosis as the next possible cause of unexplained fever. In this case if it were tuberculosis it would have to be miliary tuberculosis. There is very little evidence one way or the other on that point. After seven weeks I should think that an x-ray picture would show some disturbance in the lungs. There is an old focus from which miliary tuberculosis might have arisen from the glands in the abdomen but I would expect there would be something visible in the lungs in the way of miliary tuberculosis. His tuberculin test was negative. This is suggestive negative evidence but not conclusive because there are a certain number of severe overwhelming tuberculosis cases that have a negative tuberculin test.

Are there other disturbances of a nonbacterial character which could give a picture like this? We have all seen cases of lymphoma which run a fever of the septic type, usually not quite so continuous or regular as in this case. They usually have periods of fever alternating with periods of normal temperature, and usually some evidences of glandular disturbance turn up during the course of the disease; although it is possible for it to occur in the retroperitoneal glands without showing any evidence on physical examination. The duration of this for a fatal case of lymphoma is rather short and the onset is quite sudden. There is one thing about the blood picture which is rather against the terminal stage of lymphoma and that is the presence of twenty-two lymphocytes. One would expect with a lymphoma which had progressed to this point that there would be a higher percentage of polymorphonuclears and the lymphocytes would probably have decreased more. I think that diagnosis is unlikely.

We have some reason to think that this man

may have had lues. Can we connect this illness with lues in any way? There is a form of lues which runs a continuous septic fever; that is, syphilis of the liver. There again it is not usually a continuous fever, usually periods of fever alternating with periods of normal temperature. We have a suggestion of enlarged liver both by x-ray and percussion and yet I think that disturbance of the liver of this degree should have produced either jaundice or more marked ascites early in the game out of proportion to the amount of fluid in the chest, and I would expect that there would be a definite increase in the icteric index which is not present in this case.

We know that he had quinine therapy. Is it conceivable that he could have been treated for general paresis with malaria and the thing got away from them and they were unable to cure it? I think that is exceedingly improbable. The absence of parasites in the blood and failure of quinine to produce any effect on the disease practically exclude that possibility. I think we should have had some history on that point if such were the situation.

Are there any other parasitic infections? If it were trichinosis, there would be some increase in the eosinophils which is not the situation here. Are there other forms of bacterial septicemia which we should consider? We have more than one negative blood culture which I think is not conclusive evidence of anything. It certainly does not rule out malignant endocarditis. If it were *Streptococcus hemolyticus septicemia*, I would expect that the blood culture would pick it up and I would expect also that there would be other evidence of localized sepsis appearing from time to time. No abscess was found anywhere that we had called to our attention. Could it be staphylococcus septicemia? There again I think he would show local evidence somewhere, either in the skin or kidneys and it should have been picked up by blood culture. The meningococcus is more prevalent than usual in the community this year. Could he have had a meningococcus septicemia? That is a rare disease in its subacute form. In the acute form it usually kills within a few days. But there is a form that goes several weeks or months. The organisms are hard to grow and do not show up unless on special media. Usually skin eruptions show up during the course of the disease. Could he have had a gonococcus septicemia? There again it is a rare form of septicemia, grown only on special media. Usually if the gonococcus gets into the blood stream it is apt to cause severe ulcerative lesions of the heart valves which would cause heart murmurs, and that is not the situation here. I do not believe we can diagnose either of these latter conditions but neither can we absolutely exclude them. On the whole, I think the diagnosis which best fits the picture is that of bacterial endocarditis due to a nonhemolytic streptococcus.

DR. MALLORY: Are there any other suggestions as to diagnosis?

DR. WYMAN RICHARDSON: I wonder if Dr. Townsend would agree to the suggestion that the anemia might be a myelocytic type of anemia rather than one due to sepsis? I should like to suggest a possible diagnosis of acute aleukemic leukemia.

DR. TOWNSEND: I did not mention that. Lymphatic leukemia I should include in the lymphomatous group of diseases. I suppose myelogenous leukemia with normal white count is a possibility. It is unusual for it to run as steady and marked a fever as this. It would be consistent with the hemorrhages in the retina. This idea had occurred to me but I did not entertain it very long, particularly as I hitched up the myelocytes with the increased young forms of polymorphonuclears in the blood. I would rather expect that there would be more nucleated red cells, and a more profound degree of anemia than that present here.

DR. MALLORY: I think it is fair to say that no really good blood smear was probably ever seen on the case. We finally collected one and it contained a great many so-called smudge forms which were pretty hard to identify, but some of them we thought were probably blast forms, although they evidently were not counted in the actual differentiation on the wards.

DR. GERALD BLAKE: I may tell you a word or two about the man's early symptoms because I saw him two weeks before admission to the hospital, when he had been ill for three weeks. The chief thing that troubled him up to that time was sweating. He had four to six drenching sweats in twenty-four hours. The only case that I have seen sweat to this degree was one of dinitrophenol poisoning. He had a constant low white count between 4,600 and 6,000. He had no particular symptoms when he was not in one of the sweating periods. He had morning temperature between 100° and 102° until the day before I saw him, when it reached 104°, with a subnormal temperature on the afternoon of that day.

He was given quinine as a therapeutic test for malaria and not for any other reason. He looked well except for flushing of the face. He had no localizing signs anywhere that I could find except an inconstant left Babinski. Two weeks afterwards he was admitted to the hospital. Both at entrance and during his stay in the hospital we considered the various things that Dr. Townsend has just spoken of but could not demonstrate any one of them to our own satisfaction. He died of circulatory failure with a few localizing signs that might have been

from the central nervous system. I came to the autopsy and asked if they had found miliary tuberculosis, thinking that was the most probable diagnosis of those considered but not proved.

Clinical Diagnoses

Fever of unknown origin.
Miliary tuberculosis?

Dr. James H. Townsend's Diagnosis

Subacute bacterial endocarditis.

Anatomic Diagnoses

Aleukemic myeloid leukemia with involvement of the liver and spleen.
Hydrothorax.
Hydropericardium.
Ascites.
Peripheral edema.
Pulmonary edema, marked bilateral.
Infarct of the spleen.
Cholelithiasis.

Pathologic Diagnoses

Dr. Mallory: At the autopsy we found the various serous cavities full of fluid, nearly three liters in the chest, as much in the abdomen and generalized peripheral edema. The lungs except for edema were entirely negative. The heart was normal in size and the valves were normal. The liver was very much enlarged, weighing 2,600 grams, very pale, with rather prominent markings. The spleen was moderately enlarged, 400 grams, with numerous infarcts. The kidneys were a little large and edematous. The bone marrow showed a little wider distribution of red marrow than normally. The findings were not very striking in gross so we were still pretty much in the dark as to what he might have. Dr. Gall, having seen the blood smear a few hours before the patient's death, had become suspicious of leukemia and thought that the gross findings were consistent with an aleukemic leukemia.

The sections proved very interesting because from the bone marrow it was quite impossible to make a diagnosis of leukemia. It showed a very diffuse hyperplasia about equally distributed between the red and the white cell series with a large number of mononuclear phagocytes but the liver showed infiltration of all the sinusoids with typical leukemic cells that are obviously of the myeloid series and the same cells were present in large numbers in the spleen. Although there was no leukemic infiltration anywhere else, the only diagnosis we feel we can make is an aleukemic myeloid leukemia, with the leukemic manifestations limited to the portal circulation. I have not infrequently seen the localized type of leukemic infiltration in aleukemic lymphatic leukemia but I have not before seen it in a myeloid leukemia in which the bone marrow was not characteristic.

The postmortem blood cultures were obscured by an overgrowth of gas bacillus which I am sure is postmortem, so I cannot say that we absolutely ruled out sepsis. I cannot believe, however, that any form of sepsis would account for the findings.

A Physician: Did you examine the brain?

Dr. Mallory: Yes. It was negative except for gas bubbles.

The New England
Journal of Medicine

SUCCESSOR TO
THE BOSTON MEDICAL AND SURGICAL JOURNAL

Established in 1828

Published by THE MASSACHUSETTS MEDICAL SOCIETY under the jurisdiction of the

COMMITTEE ON PUBLICATIONS

R. I. LEE, M.D., *Chairman* HOMER GAGE, M.D.
R. B. OSGOOD, M.D. R. M. SMITH, M.D.
F. H. LAHEY, M.D.

EDITORIAL STAFF

JOHN P. SUTHERLAND, M.D. STEPHEN RUSHMORE, M.D.
GEORGE R. MINOT, M.D. HANS ZINSSER, M.D.
FRANK H. LAHEY, M.D. BENJAMIN WHITE, PH.D.
SHIELDS WARREN, M.D. HENRY R. VIETS, M.D.
GEORGE L. TOBEY, JR., M.D. ROBERT N. NYE, M.D.
C. GUY LANE, M.D. ROBERT M. GREEN, M.D.
WILLIAM A. ROGERS, M.D. CHARLES C. LUND, M.D.
JOHN F. FULTON, M.D. DWIGHT O'HARA, M.D.

ASSOCIATE EDITORS

GEORGE G. SMITH, M.D. WILLIAM B. BREED, M.D.
JOSEPH GARLAND, M.D.

WALTER P. BOWERS, M.D., *Managing Editor*
CLARA D. DAVIES, *Assistant Editor*

THE NEW HAMPSHIRE MEDICAL SOCIETY
PUBLICATION COMMITTEE

CARLETON R. METCALF, M.D. HENRY H. AMSDEN, M.D.
WARREN H. BUTTERFIELD, M.D.

THE VERMONT STATE MEDICAL SOCIETY
PUBLICATION COMMITTEE

WILLIAM G. RICKER, M.D. C. F. DALTON, M.D.
L. H. ROSS, M.D.

SUBSCRIPTION TERMS: *$6.00 per year in advance, postage paid for the United States, Canada $7.04 per year, $8.52 per year for all foreign countries belonging to the Postal Union.*

Material for early publication should be received not later than noon on Saturday. Orders for reprints must be sent to the Journal office, 8 Fenway.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to The New England Journal of Medicine, 8 Fenway, Boston, Mass.

THE NEW DIPHTHERIA

AFTER the close of the World War, diphtheria appeared in some of the countries of Central Europe in a new and malignant form. The course of the disease was rapid, the symptoms severe, and the fatality exceptionally high. Diphtheria antitoxin seemed to have lost its usual efficacy, especially in toxic disorders of the nasopharynx, which, despite abundant use of antitoxin, showed a fatality of 40 per cent or more. Later this more virulent type of the disease appeared sporadically in such great American centers as Chicago, Detroit and New York. Clinicians and bacteriologists were puzzled by the new character which the disease had assumed and believed that the Klebs-Loeffler bacillus had either undergone a marked transformation in type, or else, for some obscure reason, the organism had acquired new or exalted toxigenic properties.

Studies of the cultures isolated from fulminating cases and of the toxins produced by the bacilli revealed that the infection was caused by the same familiar diphtheria bacillus and that the toxin elaborated, because of its neutralization with specific antitoxin, differed in no way from the toxin produced in the past by well-known strains of the organism.

The assumption arose that the more rapid and violent course of the diphtheria then prevalent was due to accelerated vital activities of the bacillus and, therefore, the apparent failure of diphtheria antitoxin to mitigate the disease could be ascribed to delay and not to dosage in its administration. Paschau found that doses of antitoxin no greater than 1,000 units per kilogram of body weight were sufficient to prevent the fatality rate from rising from the old levels. When antitoxin was administered to patients in the Berlin Municipal Orphanage and Foster Home, where 80 per cent of the cases received injections within the first two days of the disease, only 1.96 per cent of the patients died, whereas in another children's hospital, in which to only 37.2 per cent of all diphtheria cases and 34.4 per cent of toxic cases was serum administered during the first two days of illness, the percentage of deaths averaged 13.3 per cent.

The answer, then, to the problem presented by the new and more malignant form of diphtheria is not a different antitoxin but antitoxin given as soon as possible after the onset of symptoms. Any case of illness, particularly in children, presenting symptoms which arouse in the physicians' minds a suspicion of diphtheria should, even before a culture is taken for bacteriological diagnosis, be given an *intramuscular* injection of at least 10,000 units of diphtheria antitoxin. The physician, who always bears in mind that in diphtheria the symptoms observed at any given time represent the delayed effect of the concentration of toxin present in the body twelve to twenty-four hours previously, will appreciate the greater urgency in giving antitoxin if patients stricken with the new diphtheria are to be saved.

REFERENCE

Berlin letter of March 19, 1936. J. A. M. A. **106**:1674 (May 9) 1936.

THE BILIOUSNESS OF GENIUS

"SICKLIED o'er with the pale cast of thought" may be a bit more than a line of poetic imagery, if one follows through the line of reasoning established by T. Wingate Todd, anatomist at Western Reserve University's School of Medicine. According to the philosophical deductions of this investigator, as detailed by the *New York Times*, genius, like an army, travels on its stomach, but what a wagon it has to hitch its star to!

Looking back into history we find that Samuel Johnson's brilliance of imagery and creative thought, as well as his cantankerous disposition, were the result of his chronic indiges-

tion; that Darwin's theory of evolution was due to the imagery created by his gastroenteric disturbances; that the facts of Conrad's experiences were sharpened and amplified by nervous dyspepsia. Less is known about Shakespeare's personal digestive ability, but we may assume that he had some basis on which to mention, in Much Ado About Nothing, Benedick's "quick wit and gueasy stomach." In fact, as we all know, intellectual attainments and peptic ulcer go hand in hand, although it may well be the brain that causes the ulcer that stimulates the brain.

As evidence Dr. Todd, having made roentgen ray studies of the healthy stomachs of more than 800 of his students, presents the conclusion that emotional states reduce the stomach's gastric waves of contraction, and cause prolonged closure of the pylorus. New students, emotionally upset by an unfamiliar experiment, had large, inactive stomachs, while in later repetitions of the experiments the same students' stomachs grew smaller and more active, indicating that the emotional stress had been eliminated. The definite relationship of these observations to genius is left to the reader's genius to deduce, although this need not be difficult; no one will deny that a stomachache sharpens the imagination.

Genius may enter into journalism, but fortunately is not a *sine qua non* of it, and it may give comfort to the *Journal's* readers to know that its Editorial Staff, collectively and individually, is blessed with excellent digestion.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

STEWART, JOHN D. B.A., M.D. Harvard University Medical School 1928. Assistant in Surgery, and Dalton Scholar, Massachusetts General Hospital. His subject is Fluid Therapy in Surgery: A Critical Review. Page 53. Address: Massachusetts General Hospital, Boston, Mass.

HUDSON, HENRY W., JR. M.D. Harvard University Medical School 1925. F.A.C.S. Associate Surgeon, Children's Hospital. Assistant in Surgery, Harvard University Medical School. Address: 1101 Beacon Street, Brookline, Mass. Associated with him is

KRAKOWER, CECIL. M.D., M.C. McGill University Medical School 1932. Acting Pathologist, Children's Hospital, 1935-36. Address: School of Tropical Medicine, San Juan, Puerto Rico. Their subject is Acute Appendicitis and Measles. Page 59.

RISEMAN, JOSEPH E. F. B.S., M.D. Harvard University Medical School 1929. Assistant in Medicine, Harvard University Medical School 1931-. Research Associate, Beth Israel Hospital, 1931-. Assistant Physician, Beth Israel Hospital, 1936-. Address: Beth Israel Hospital, Boston, Mass. Associated with him is

LESNICK, GERSON. B.S. Harvard University Medical School, Class of 1937. Address: Beth Israel Hospital, Boston, Mass. Their subject is A Simple Method of Oxygen Analysis for Use in Oxygen Tent Therapy. Page 65.

HOOKER, SANFORD B. A.B., A.M., M.D. Boston University School of Medicine 1913. Member, Evans Memorial. Immunologist, Massachusetts Memorial Hospitals. Professor of Immunology, Boston University School of Medicine. His subject is The Plurality of Streptococcal Toxins. Page 68. Address: 80 East Concord Street, Boston, Mass.

LAMBERT, ALEXANDER. M.D. Columbia University of Physicians and Surgeons 1888. Formerly, Professor of Clinical Medicine, Cornell University Medical School; Attending Physician, Bellevue Hospital; and President of the American Medical Association. His subject is Therapeutics of Drug Habits. Page 72. Address: 43 East 72nd Street, New York City.

ELEY, R. CANNON. M.D. Medical Department, University of Virginia 1925. Associate in Pediatrics and Communicable Diseases, Harvard University Medical School and School of Public Health. Associate Visiting Physician, Children's Hospital, Boston. His subject is Advances in Pediatrics. Page 82. Address: 319 Longwood Avenue, Boston, Mass.

MISCELLANY

AN HONOR TO DR. W. B. CASTLE

Among the scientists receiving honorary degrees from Utrecht University, the name of William Bosworth Castle appears. According to a wireless message to the *New York Times-Boston Herald*, he was made a Doctor of Medicine on June 24 on the occasion of the Tercentenary of the University.

Dr. Castle received his M.D. degree from the Harvard Medical School in 1921. He holds the position of Associate Professor of Medicine in the Harvard Medical School and is Associate Director of the Thorndike Memorial Laboratory of the Boston City Hospital. During 1931 he was Director of the Commission of the Rockefeller Foundation for the Study of Anemia in Puerto Rico.

Dr. Castle and his associates have conducted research work concerned especially with the etiology and treatment of pernicious anemia and related macrocytic anemias, including sprue.

APPOINTMENTS BY THE HARVARD UNIVERSITY FACULTY

For three years Dr. Robert M. Green, associate professor of applied anatomy; Dr. Charles F. McKhann, associate professor of pediatrics and communicable diseases; Dr. Jacob E. Finesinger, assistant professor of psychiatry; Dr. William G. Lennox, assistant professor of neurology; Dr. Henry R. Viets, associate in neurology and Dr. Harry C. Solomon, associate professor of psychiatry.

OBITUARIES

RICHARD GOODWIN WADSWORTH, A.B., M.D.

JUNE 30, 1874-JULY 4, 1936

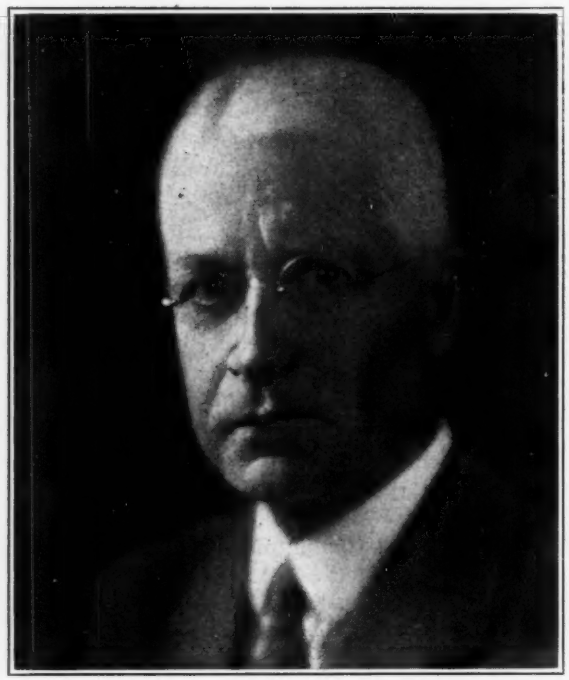


Photo by Bachrach

Richard Goodwin Wadsworth was a lineal descendant of Peleg Wadsworth, General in the War of Independence, and was born in Boston, the son of Dr. Oliver Fairfield Wadsworth, Professor of Ophthalmology at Harvard, and Mary Chapman (Goodwin) Wadsworth. Preparing for Harvard at the Hopkinson School, he received his A.B. in 1896 and his M.D. in 1900. He was appointed Surgical House Officer to the Massachusetts General Hospital from 1899 to 1901. On June 25, 1901, he married Mary Heath Atkinson of Brookline and in the same year was made an Assistant Surgeon to Out-Patients at the Brookline Free Hospital for Women. This hospital he served until his death as Surgeon to Out-Patients, Assisting Visiting Surgeon, Resident Pathologist and member of the Consulting Staff. The Harvard Medical School appointed him an Assistant in Anatomy in 1903, a Fellow in Gynecology in 1913, and an Instructor in Gynecology in 1929. He was a Fellow of the American College of Surgeons and of the American Medical Association, a member of the Massachusetts Medical Society, the Boston Obstetrical Society, the Bigelow Club and many other medical organizations. For twenty years he was Secretary-Treasurer of the Boston Medical Library, and for sixteen years the President of the Elizabeth Peabody House. In the Great War he was medical adviser to the New England Division of the American Red Cross and Chairman of the Committee on First Aid. He had been Secretary of his medical school class since graduation and was elected President for the Tercentenary Year. His clubs were the Tavern, the Tennis and Racquet, and The Country Club of Brookline.

Francesca Alexander has versified an Italian folklore story called "The Hidden Servants." An humble hermit who has striven hard to be good asks God to show him other living men who have become as holy as he, hoping in his heart that they may prove to be bishops or even cardinals. His prayer is answered but the answer surprises him. The other human beings of equal sanctity are discovered to be several simple folk who hold no religious office. After he has learnt their story and they have shyly told him their deeds, he realizes that the world holds many quiet people who are serving their God and their fellowmen as truly as those in the exalted orders of the Church.

Richard Wadsworth's service was not hidden; the light of his candle was too bright, but he never held the candlestick himself. His sterling worth and great ability were sometimes not fully realized by those who did not come into close contact with his character. An exquisite humility satisfied Saint Paul's description of charity, "which suffereth long and is kind . . . envieth not, vaunteth not itself, . . . doth not behave itself unseemly, seeketh not her own, is not easily provoked, thinketh no evil." "Charity never faileth," nor did this servant of men and women and medicine fail to fulfil every trust he accepted.

The richness of his nature was revealed to all those who came into contact with him, once his gentle reserve was broken. This was true whether one knew him as a skilful golfing companion or as an intimate in a small medical club, as a member of the staff of a great hospital or as treasurer of the Boston Medical Library and the Boston Health League. The latter organization he had served since its incorporation in 1922 and its balanced budget is due to his financial wisdom. He insisted upon keeping the complicated double entry books himself in order to save expense and these were in complete order at the time of his death.

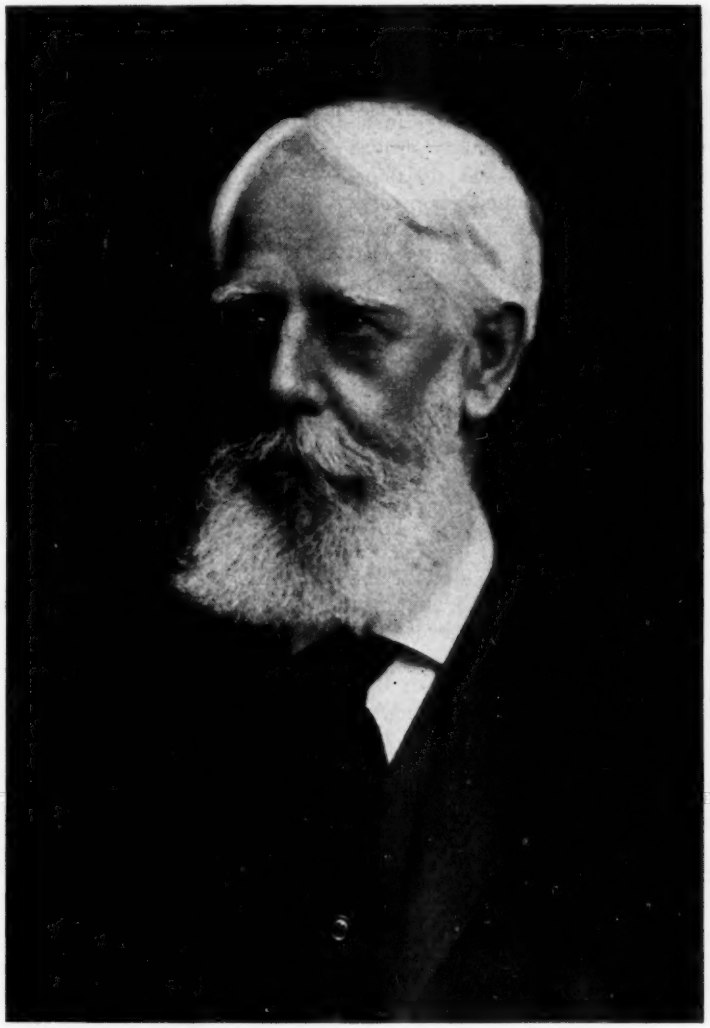
There was an aura about him of sweetness and strength, of efficiency and skill, of unselfishness and courage. His modesty in both speaking and writing may have limited his practice numerically but there was no limit to the confidence he inspired in those who came under his care. He made the poor and those seriously ill his special charges. His surgical results rank with the very best. A patient whose life he has recently saved and made happy by a dif-

ficult surgical procedure has revealed the completeness of his self-effacement. He attended the birth of her daughter on the same day that his own child died, yet there was no suspicion aroused in her mind of the acute sadness in his.

Honors meant nothing to him, usefulness everything. He was nobly born into a family eminent in medicine and public service and was worthy of this heritage. To the humblest of his helpers he showed as genuine a courtesy as to the richest of his patients. The institutions which he served so faithfully and diligently will continue to owe him large debts. These will be lessened by the tribute of gratitude paid by the great company of men and women whose burdens he lightened and whose lives were touched by his spirit.

R. B. O.

FRANCIS H. WILLIAMS, M.D.



Dr. Francis H. Williams of Boston, widely known for the important part which he played in introducing and developing the use of the roentgen rays for medical purposes, died on June 22, 1936, at the age of eighty-four years.

He was born in Uxbridge, Mass., April 15, 1852, the son of Henry Willard and Elizabeth (Dewe) Williams. In 1873 he graduated with the degree of B.S. from the Massachusetts Institute of Technology. In 1874 he was a member of the Transit of Venus Expedition to Japan. After his graduation from the Harvard Medical School in 1877 he spent two years of study in Europe. In 1879 he entered upon the practice of medicine in Boston, and almost at once was appointed to the Staff of the Boston City Hospital, where most of his important work was accomplished.

Always a pioneer, and in advance of others in seeing the possibilities of new methods, Dr. Williams is to be credited with notable achievements apart from the field of the roentgen rays. He was one of the first to test blood-pressure, using an instrument of his own invention. In the years 1884 to 1891 he gave instruction in therapeutics at the Har-

vard Medical School, and some of his teachings, as in the use of digitalis, were in advance of his time. He was among the first teachers of medicine to introduce bedside instruction to small groups of students. He initiated bacteriological examinations in cases of suspected diphtheria, and was the first in the community to use antitoxin in the treatment of that disease. These achievements, however, merely illustrate his exceptional ability, which found its great opportunity in this new field of radiology.

In December, 1895, Roentgen, a physicist, announced his discovery of "a new kind of rays," without reference to their potential uses in medicine. During the first few months of 1896 Dr. Williams made x-ray pictures in the Rogers Laboratory of Physics of the Massachusetts Institute of Technology, and soon established at the Boston City Hospital an x-ray department which immediately proved its usefulness for medical and surgical examinations. Before the end of 1896 he had examined some forty cases of pulmonary tuberculosis and had demonstrated by means of plates the value of roentgen examinations in various diseases of the heart and lungs. In 1897, using the technique employed by Dr. Walter B. Cannon in laboratory animals, he originated the clinical examinations of the digestive tract by the method followed today. In the field of treatment he was the first to prove, in a case of cancer of the lip, that cancer could be cured by the roentgen rays without destruction of the surrounding tissues. He was very early impressed with the danger to the operator of too long exposure to x-light, and, by means of safeguards which he devised, he alone among the early workers in New England escaped permanent injury or death. In this unknown subject much attention was necessarily devoted to the development of apparatus; in this he was greatly aided by his brother-in-law, William Herbert Rollins, and by fellow-workers in electrical science at the Massachusetts Institute of Technology. In 1901 he published his book, "The Roentgen Rays in Medicine and Surgery," which stands as a classic in its subject. Throughout the world of radiology it is recognized that to Dr. Williams is due a large share of the credit for the medical applications of Roentgen's discovery.

The discovery of radium opened a new field for investigation which Dr. Williams was one of the first to enter. Here again the X-Ray Department of the Boston City Hospital, which he founded in 1896, and of which he remained the head until his resignation in 1915, became a center for advanced clinical research. The results of thirty years' experience in the use of radium, beginning in 1903, are embodied in his book, "Radium Treatment of Skin Diseases, New Growths, Diseases of the Eyes and Tonsils," published in 1935.

In personality he was a forceful figure, conspicuous for his zeal for the truth. He was essentially an individual worker, preferring to associate with a few close friends of similar tastes rather than with the many. Yet by those whose privilege it was to know him well, and especially by his younger assistants at the hospital, he was admired and beloved.

He was a Fellow of the American Academy of Arts and Sciences, a Fellow of the Massachusetts Medical Society, the American Medical Association, and many other societies both in this country and in Europe. In 1918 he was President of the Association of American Physicians. He was an honorary member of the American Radium Society, American Roentgen Society, and the Radiological Society of North America. Always a loyal alumnus of the Massachusetts Institute of Technology, in 1882 he was elected to life membership in the Corporation, and for the first twenty-five years of its existence was a member of the Executive Committee.

In 1891 Dr. Williams married Anna Dunn Phillips, a granddaughter of the first Mayor of Boston. There were no children.

RECENT DEATHS

JOHNSTON—Charles Edward Johnston, M.D., of 110 Court Street, Portsmouth, New Hampshire, died in that city June 28, 1936.

Dr. Johnston was born in 1864 and graduated from the Dartmouth Medical School in 1897. He was a former member of the city council, the Portsmouth and State Medical Societies, and the Scottish Clans.

During the World War Dr. Johnston served in the medical corps with the rank of captain.

He is survived by his widow, a brother and three sisters.

LUNDGREN—Albert Gustaf Lundgren, M.D., of 65 Rosewood Street, Mattapan, died June 28, 1936, at Pocasset.

Dr. Lundgren was born in Worcester, Massachusetts, in 1892. He was a graduate of Clark University, and of Boston University School of Medicine (1933). He served as resident physician at the Evans Memorial Hospital in 1934 and 1935 and was a veteran of the World War.

Dr. Lundgren is survived by his widow, Mrs. Mabel Johnson Lundgren; two sons, his mother and four sisters.

GALLAGHER—James Thomas Gallagher, M.D., of 20 Monument Square, Charlestown District, Boston, died at his home June 30, 1936.

Dr. Gallagher was eighty-three years of age at the time of his death. He was born in County Sligo, Ireland, and graduated from Trinity College in Dublin.

He came to America in 1892 and studied medicine at the Bellevue Hospital Medical College. After practicing in Salem, Massachusetts for several years, he moved to Charlestown and organized the Charlestown Medical Society.

Dr. Gallagher was a member of the Guild of St. Luke and the Charitable Irish Society of New York.